PCT



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A2 (11) International Publication Number: WO 00/31258 (43) International Publication Date: 02 June 2000 (02.06.2000) C12N 15/12, C07K 14/72 PCT/US99/23687 (21) International Application Number: **Published** (22) International Filing Date: 13 October 1999 (13.10.1999) (30) Priority Data: 09/416,760 12 October 1999 (12.10.1999) US 12 October 1999 (12.10.1999) US 09/417,044 20 November 1998 (20.11.1998) US 60/109,213 16 February 1999 (16.02.1999) US 60/120,416 26 February 1999 (26.02.1999) US 60/121.852 12 March 1999 (12.03.1999) US 60/123,946 60/123,949 12 March 1999 (12.03.1999) US 28 May 1999 (28.05.1999) US 60/136,436 60/136,437 28 May 1999 (28.05.1999) US 28 May 1999 (28.05.1999) US 60/136,439 60/136.567 28 May 1999 (28.05.1999) US 28 May 1999 (28.05.1999) US 60/137,127 28 May 1999 (28.05.1999) US 60/137,131 60/141,448 30 June 1999 (30.06.1999) US 29 September 1999 (29.09.1999) US 60/156,555 29 September 1999 (29.09.1999) US 60/156,633 60/156,634 29 September 1999 (29.09.1999) US 29 September 1999 (29.09.1999) US 60/156.653 01 October 1999 (01.10.1999) US 60/157,280 01 October 1999 (01.10.1999) US 60/157,281 60/157,282 01 October 1999 (01.10.1999) US 01 October 1999 (01.10.1999) US 60/157,293 60/157,294 01 October 1999 (01.10.1999) US (60) Parent Application or Grant ARENA PHARMACEUTICALS, INC. [/]; (). CHEN, Ruoping [/]; (). DANG, Huong, T. [/]; (). LIAW, Chen, W. [/]; (). LIN, I-Lin [/]; (). CHEN, Ruoping [/]; (). DANG, Huong, T. [/]; (). LIAW, Chen, W. [/]; (). LIN, I-Lin [/]; (). MILLER, Suzanne, E.; ().

(54) Title: HUMAN ORPHAN G PROTEIN-COUPLED RECEPTORS

(54) Titre: RECEPTEURS HUMAINS COUPLES A LA PROTEINE G ORPHAN

(57) Abstract

The invention disclosed in this patent document relates to transmembrane receptors, more particularly to endogenous, human orphan G protein-coupled receptors.

(57) Abrégé

L'invention porte sur des récepteurs transmembranaires, et plus spécifiquement sur des récepteurs endogènes, humains, couplés à la protéine G orphan.

- 4

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7:		(11) International Publication Number: WO 00/3125
C12N 15/12, C07K 14/72	A2	(43) International Publication Date: 2 June 2000 (02.06.00
(21) International Application Number: PCT/U	S99/236	09/416,760 12 October 1999 (12.10.99) U
(30) Priority Data: 60/109,213 60/120,416 16 February 1999 (16.02.9 60/121,852 26 February 1999 (26.02.9 60/123,946 12 March 1999 (12.03.99) 60/136,436 28 May 1999 (28.05.99) 60/136,437 28 May 1999 (28.05.99) 60/136,437 28 May 1999 (28.05.99) 60/136,567 28 May 1999 (28.05.99) 60/137,127 28 May 1999 (28.05.99) 60/137,127 28 May 1999 (28.05.99) 60/137,131 28 May 1999 (28.05.99) 60/136,633 29 September 1999 (29.06.99) 60/156,633 29 September 1999 (29.09.09) 60/156,634 29 September 1999 (29.09.09) 60/157,280 60/157,281 1 October 1999 (01.10.99) 60/157,282 1 October 1999 (01.10.99)	.98)	(71) Applicant (for all designated States except US): AREN. PHARMACEUTICALS, INC. [US/US]; 6166 Nancy Ridg Drive, San Diego, CA 92121 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CHEN, Ruoping [CN/US 5296 Timber Branch Way, San Diego, CA 92130 (US DANG, Huong, T. [US/US]; 5352 Oak Park Drive, Sa Diego, CA 92105 (US). LIAW, Chen, W. [US/US]; 766 Salix Place, San Diego, CA 92129 (US). LIN, 1-Lin [-/US 8291-7 Gold Coast Drive, San Diego, CA 92126 (US). (74) Agents: MILLER, Suzanne, E. et al.; Woodcock Washbur Kurtz Mackiewicz & Norris LLP, 46th floor, One Libert Place, Philadelphia, PA 19103 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BC BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EI ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, IJ KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MAD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UC US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM, TM, TM, TM, TM, TM, TM,

(57) Abstract

The invention disclosed in this patent document relates to transmembrane receptors, more particularly to endogenous, human orphan G protein-coupled receptors.

••4

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	I.U	Luxembourg	SN	Senegal
ΑU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
ΑZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	'GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	1T	Trinidad and Tobago
ВJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	บร	United States of America
CA	Canada	lТ	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Vict Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugostavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	zw	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korca	PT	Portugal		
CU	Cuba	KZ	Kazakstan	кo	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Pederation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	ŠG	Singapore		

Description

THIS PAGE BLANK (USPTO)

• ``3

10

15

20

25

30

35

40

45

50

55

HUMAN ORPHAN G PROTEIN-COUPLED RECEPTORS

This patent document claims priority benefit of each of the following applications, all filed with the United States Patent and Trademark Office via U.S. Express Mail on the 5 indicated filing dates: U.S. Provisional Number 60/121,852, filed; February 26, 1999 claiming the benefit of U.S. Provisional Number 60/109,213, filed November 20, 1998; U.S. Provisional Number 60/120,416, filed February 16, 1999; U.S. Provisional Number 60/123,946, filed March 12, 1999; U.S. Provisional Number 60/123,949, filed March 12, 1999; U.S. Provisional Number 60/136,436, filed May 28, 1999; U.S. Provisional 10 Number 60/136,439, filed May 28, 1999; U.S. Provisional Number 60/136,567, filed May 28, 1999; U.S. Provisional Number 60/137,127, filed May 28, 1999; U.S. Provisional Number 60/137,131, filed May 28, 1999; U.S. Provisional Number 141,448, filed June 29, 1999 claiming priority from U.S. Provisional Number 60/136,437, filed May 28, 1999; U.S. Provisional Number _____ (Arena Pharmaceuticals, Inc. docket number 15 CHN10-1), filed September 29, 1999; U.S. Provisional Number 60/156,333, filed September 29, 1999; U.S. Provisional Number 60/156,555, filed September 29, 1999; U.S. Provisional Number 60/156,634, filed September 29, 1999; U.S. Provisional Number _____ (Arena Pharmaceuticals, Inc. docket number RUP6-1), filed October 1, 1999; U.S. Provisional Number _____ (Arena Pharmaceuticals, Inc. docket number 20 RUP7-1), filed October 1, 1999; U.S. Provisional Number _____ (Arena Pharmaceuticals, Inc. docket number CHN6-1), filed October 1, 1999; U.S. Provisional

Number ______ (Arena Pharmaceuticals, Inc. docket number RUP5-1), filed October 1, 1999; U.S. Provisional Number ______ (Arena Pharmaceuticals, Inc. docket number CHN9-1), filed October 1, 1999. This patent document is related to U.S. Serial Number 09/170,496 filed October 13, 1998, and U.S. Serial Number unknown (Woodcock 5 Washburn Kurtz Mackiewicz & Norris, LLP docket number AREN-0054) filed on October 12, 1999 (via U.S. Express Mail) both being incorporated herein by reference.

This patent document also is related to U.S. Serial No. 09/364,425; filed July 30, 1999, which is incorporated by reference in its entirety. This application also claims priority to U.S. Serial Number _____ (Woodcock, Washburn, Kurtz, Makiewicz & Norris, LLP 10 docket number AREN-0050), filed on October 12, 1999 (via U.S. Express Mail), incorporated by reference herein in its entirety. Each of the foregoing applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention disclosed in this patent document relates to transmembrane receptors, 15 and more particularly to endogenous, orphan, human G protein-coupled receptors ("GPCRs").

BACKGROUND OF THE INVENTION

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR or GPCRs) 20 class. It is estimated that there are some 100,000 genes within the human genome, and of these, approximately 2% or 2,000 genes, are estimated to code for GPCRs. Receptors, including GPCRs, for which the endogenous ligand has been identified are referred to as "known" receptors, while receptors for which the endogenous ligand has not been identified

45

15

20

25

30

35

40

45

50

55

are referred to as "orphan" receptors. GPCRs represent an important area for the development of pharmaceutical products: from approximately 20 of the 100 known GPCRs, 60% of all prescription pharmaceuticals have been developed. This distinction is not merely semantic, particularly in the case of GPCRs. Thus, the orphan GPCRs are to the 5 pharmaceutical industry what gold was to California in the late 19th century - an opportunity to drive growth, expansion, enhancement and development.

- 3 -

GPCRs share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane (each span is identified by number, i.e., transmembrane-1 (TM-1), 10 transmebrane-2 (TM-2), etc.). The transmembrane helices are joined by strands of amino acids between transmembrane-2 and transmembrane-3, transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or "extracellular" side, of the cell membrane (these are referred to as "extracellular" regions 1, 2 and 3 (EC-1, EC-2 and EC-3), respectively). The transmembrane helices are also joined 15 by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and transmembrane-5 and transmembrane-6 on the interior, or "intracellular" side, of the cell membrane (these are referred to as "intracellular" regions 1, 2 and 3 (IC-1, IC-2 and IC-3), respectively). The "carboxy" ("C") terminus of the receptor lies in the intracellular space within the cell, and the "amino" ("N") terminus of the receptor 20 lies in the extracellular space outside of the cell.

Generally, when an endogenous ligand binds with the receptor (often referred to as "activation" of the receptor), there is a change in the conformation of the intracellular region that allows for coupling between the intracellular region and an intracellular "G-protein." It

PCT/US99/23687 5

10

15

20

25

30

35

40

45

50

55

has been reported that GPCRs are "promiscuous" with respect to G proteins, i.e., that a GPCR can interact with more than one G protein. See, Kenakin, T., 43 Life Sciences 1095 (1988). Although other G proteins exist, currently, Gq, Gs, Gi, and Go are G proteins that have been identified. Endogenous ligand-activated GPCR coupling with the G-protein 5 begins a signaling cascade process (referred to as "signal transduction"). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition. It is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G protein.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium 10 between two different conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response. A receptor may be stabilized in an active state by an endogenous ligand or a compound such 15 as a drug.

SUMMARY OF THE INVENTION

Disclosed herein are human endogenous orphan G protein-coupled receptors.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B provide reference "grids" for certain dot-blots provided herein 20 (see also, Figure 2A and 2B, respectively).

Figures 2A and 2B provide reproductions of the results of certain dot-blot analyses resulting from hCHN3 and hCHN8, respectively (see also, Figures 1A and 1B, respectively).

Figure 3 provides a reproduction of the results of RT-PCR analysis of hRUP3.

10

15

20

25

30

35

40

45

Figure 4 provides a reproduction of the results of RT-PCR analysis of hRUP4.

Figure 5 provides a reproduction of the results of RT-PCR analysis of hRUP6.

DETAILED DESCRIPTION

The scientific literature that has evolved around receptors has adopted a number of 5 terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control:

AMINO ACID ABBREVIATIONS used herein are set out in Table 1:

10		TABLE 1	
	ALANINE	ALA	A
	ARGININE	ARG	R
	ASPARAGINE	ASN	N
	ASPARTIC ACID	ASP	D
15	CYSTEINE	CYS	С
	GLUTAMIC ACID	GLU	Е
	GLUTAMINE	GLN	Q .
	GLYCINE	GLY	Ĝ
	HISTIDINE	HIS	Н
20	ISOLEUCINE	ILE	1
	LEUCINE	LEU	L
	LYSINE	LYS	K
	METHIONINE	MET	M
	PHENYLALANINE	PHE	F
25	PROLINE	PRO	P
	SERINE	SER	s
	THREONINE	THR	T
	TRYPTOPHAN	TRP	w
	TYROSINE	TYR	Y
30	VALINE	VAL	v

COMPOSITION means a material comprising at least one component.

ENDOGENOUS shall mean a material that a mammal naturally produces.

ENDOGENOUS in reference to, for example and not limitation, the term "receptor," shall mean that which is naturally produced by a mammal (for example, and not limitation, a

50

55

. ``3

5

15

20

25

30

35

40

45

50

55

human) or a virus. By contrast, the term **NON-ENDOGENOUS** in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus.

HOST CELL shall mean a cell capable of having a Plasmid and/or Vector 5 incorporated therein. In the case of a prokaryotic Host Cell, a Plasmid is typically replicated as a autonomous molecule as the Host Cell replicates (generally, the Plasmid is thereafter isolated for introduction into a eukaryotic Host Cell); in the case of a eukaryotic Host Cell, a Plasmid is integrated into the cellular DNA of the Host Cell such that when the eukaryotic Host Cell replicates, the Plasmid replicates. Preferably, for the purposes of the invention 10 disclosed herein, the Host Cell is eukaryotic, more preferably, mammalian, and most preferably selected from the group consisting of 293, 293T and COS-7 cells.

LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

NON-ORPHAN RECEPTOR shall mean an endogenous naturally occurring 15 molecule specific for an endogenous naturally occurring ligand wherein the binding of a ligand to a receptor activates an intracellular signaling pathway.

ORPHAN RECEPTOR shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has not been identified or is not known.

PLASMID shall mean the combination of a Vector and cDNA. Generally, a Plasmid 20 is introduced into a Host Cell for the purposes of replication and/or expression of the cDNA as a protein.

VECTOR sin reference to cDNA shall mean a circular DNA capable of incorporating at least one cDNA and capable of incorporation into a Host Cell.

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

Identification of Human GPCRs

The efforts of the Human Genome project have led to the identification of a plethora of information regarding nucleic acid sequences located within the human genome; it has been the case in this endeavor that genetic sequence information has been made available without an understanding or recognition as to whether or not any particular genomic sequence does or may contain open-reading frame information that translate human proteins.

10 Several methods of identifying nucleic acid sequences within the human genome are within the purview of those having ordinary skill in the art. For example, and not limitation, a variety of GPCRs, disclosed herein, were discovered by reviewing the GenBankTM database, while other GPCRs were discovered by utilizing a nucleic acid sequence of a GPCR, previously sequenced, to conduct a BLASTTM search of the EST database. Table A, below, 15 lists the disclosed endogenous orphan GPCRs along with a GPCR's respective homologous GPCR:

	-		TABLE A		
	Disclosed	Accession	Open Reading	Per Cent	Reference To
	Human	Number	Frame	Homology	Homologous
20	Orphan	ldentified	(Base Pairs)	To Designated	GPCR
	GPCRs			GPCR	(Accession No.)
	hARE-3	AL033379	1,260 bp	52.3% LPA-R	U92642
	hARE-4	AC006087	1,119 bp	36% P2Y5	AF000546

		WO 00/31258				PCT/US99/23687
5				-8-		
		hARE-5	AC006255	1,104 bp	32% Oryzias	D43633
					latipes	
10		hGPR27	AA775870	1,128 bp		
		hARE-1	A1090920	999 bp	43%	D13626
					KIAA0001	
		hARE-2	AA359504	1,122 bp	53% GPR27	
	5	hPPR1	H67224	1,053 bp	39% EBI1	L31581
15		hG2A	AA754702	1,113 bp	31% GPR4	L36148
		hRUP3	AL035423	1,005 bp	30%	2133653
					Drosophila	
00					melanogaster	
20		bRUP4	AI307658	1,296 bp	32% pNPGPR	NP_004876
					28% and 29 %	AAC41276
,					Zebra fish Ya	and
25					and Yb,	AAB94616
					respectively	
		hRUP5	AC005849	1,413 bp	25% DEZ	Q99788
30					23% FMLPR	P21462
30	10	hRUP6	AC005871	1,245 bp	48% GPR66	NP_006047
		hRUP7	AC007922	1,173 bp	43% H3R	AF140538
		hCHN3	EST 36581	1,113 bp	53% GPR27	
		hCHN4	AA804531	1,077 bp	32% thrombin	4503637
		hCHN6	EST 2134670	1,503 bp	36% edg-1	NP_001391
35	15	hCHN8	EST 764455	1,029 bp	47%	D13626
		-			KIAA0001	
		hCHN9	EST 1541536	1,077 bp	41% LTB4R	NM_000752
		hCHN10	EST 1365839	1,055 bp	35% P2Y	NM_002563

Receptor homology is useful in terms of gaining an appreciation of a role of the disclosed receptors within the human body. Additionally, such homology can provide insight 20 as to possible endogenous ligand(s) that may be natural activators for the disclosed orphan GPCRs.

B. Receptor Screening

Techniques have become more readily available over the past few years for

55

40

45

5

45

50

55

endogenous-ligand identification (this, primarily, for the purpose of providing a means of conducting receptor-binding assays that require a receptor's endogenous ligand) because the traditional study of receptors has always proceeded from the a priori assumption (historically based) that the endogenous ligand must first be identified before discovery could proceed to 5 find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been heretofore recognized is that it is the active state of the receptor that is most useful for discovering agonists, partial 10 agonists, and inverse agonists of the receptor. For those diseases which result from an overly active receptor or an under-active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor or enhance the activity of the receptor, respectively, not necessarily a drug which is an antagonist to the endogenous ligand. This is because a compound that reduces or enhances the activity of the active receptor state 15 need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state.

As is known in the art, GPCRs can be "active" in their endogenous state even without the binding of the receptor's endogenous ligand thereto. Such naturally-active receptors can 20 be screened for the direct identification (i.e., without the need for the receptor's endogenous ligand) of, in particular, inverse agonists. Alternatively, the receptor can be "activated" via, e.g., mutation of the receptor to establish a non-endogenous version of the receptor that is active in the absence of the receptor's endogenous ligand.

Screening candidate compounds against an endogenous or non-endogenous, constitutively activated version of the human orphan GPCRs disclosed herein can provide for the direct identification of candidate compounds which act at this cell surface receptor, without requiring use of the receptor's endogenous ligand. By determining areas within 5 the body where the endogenous version of human GPCRs disclosed herein is expressed and/or over-expressed, it is possible to determine related discase/disorder states which are associated with the expression and/or over-expression of the receptor; such an approach is disclosed in this patent document.

With respect to creation of a mutation that may evidence constitutive activation of 10 human orphan GPCRs disclosed herein is based upon the distance from the proline residue at which is presumed to be located within TM6 of the GPCR typically nears the TM6/IC3 interface (such proline residue appears to be quite conserved). By mutating the amino acid residue located 16 amino acid residues from this residue (presumably located in the IC3 region of the receptor) to, most preferably, a lysine residue, such activation may be obtained. 15 Other amino acid residues may be useful in the mutation at this position to achieve this objective.

C. Disease/Disorder Identification and/or Selection

Preferably, the DNA sequence of the human orphan GPCR can be used to make a probe for (a) dot-blot analysis against tissue-mRNA, and/or (b) RT-PCR identification of 20 the expression of the receptor in tissue samples. The presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be preferably utilized to identify a correlation with a treatment regimen, including but not limited to, a disease associated

10

15

25

20

30

35

40

45

50

55

- 11 -

with that disease. Receptors can equally well be localized to regions of organs by this technique. Based on the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.

D. Screening of Candidate Compounds

5 1. Generic GPCR screening assay techniques

When a G protein receptor becomes constitutively active (i.e., active in the absence of endogenous ligand binding thereto), it binds to a G protein (e.g., Gq, Gs, Gi, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes 10 deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of GTP, [35S]GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors. It is reported that [35S]GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and 15 available to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay system is for initial screening of candidate compounds because the system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

2. Specific GPCR screening assay techniques

Once candidate compounds are identified using the "generic" G protein-coupled receptor assay (i.e., an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is preferred. For example, a compound identified by the "generic" assay may not bind to the

receptor, but may instead merely "uncouple" the G protein from the intracellular domain.

- 12 -

a. Gs and Gi

10

15

20

25

30

35

40

45

50

55

Gs stimulates the enzyme adenylyl cyclase. Gi (and Go), on the other hand, inhibit this enzyme. Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, 5 constitutively activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple the Gi (or Go) protein are associated with decreased cellular levels of cAMP. See, generally, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Thus, assays that detect cAMP can 10 be utilized to determine if a candidate compound is, e.g., an inverse agonist to the receptor (i.e., such a compound would decrease the levels of cAMP). A variety of approaches known in the art for measuring cAMP can be utilized; a most preferred approach relies upon the use of anti-cAMP antibodies in an ELISA-based format. Another type of assay that can be utilized is a whole cell second messenger reporter system assay. Promoters on genes drive 15 the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or transcription factor (CREB) which then binds to the promoter at specific sites called cAMP response elements and drives the expression of the gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter 20 gene, e.g., β-galactosidase or luciferase. Thus, a constitutively activated Gs-linked receptor causes the accumulation of cAMP that then activates the gene and expression of the reporter protein. The reporter protein such as β-galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995).

Go and Gq.

Gq and Go are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid PIP₂, releasing two intracellular messengers: 5 diacycloglycerol (DAG) and inistol 1,4,5-triphoisphate (IP₃). Increased accumulation of IP₃ is associated with activation of Gq- and Go-associated receptors. See, generally, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Assays that detect IP₃ accumulation can be utilized to determine if a candidate compound is, e.g., an inverse agonist to a Gq- or Go-10 associated receptor (i.e., such a compound would decrease the levels of IP₃). Gq-associated receptors can also been examined using an AP1 reporter assay in that Gq-dependent phospholipase C causes activation of genes containing AP1 elements; thus, activated Gq-associated receptors will evidence an increase in the expression of such genes, whereby inverse agonists thereto will evidence a decrease in such expression, and agonists will 15 evidence an increase in such expression. Commercially available assays for such detection are available.

3. GPCR Fusion Protein

The use of an endogenous, constitutively activated orphan GPCR, or a non-endogenous, constitutively activated orphan GPCR, for screening of candidate compounds 20 for the direct identification of inverse agonists, agonists and partial agonists provides a unique challenge in that, by definition, the receptor is active even in the absence of an endogenous ligand bound thereto. Thus, it is often useful that an approach be utilized that can enhance the signal obtained by the activated receptor. A preferred approach is the use of a GPCR Fusion Protein.

Generally, once it is determined that a GPCR is or has been constitutively activated, using the assay techniques set forth above (as well as others), it is possible to determine the predominant G protein that couples with the endogenous GPCR. Coupling of the G protein to the GPCR provides a signaling pathway that can be assessed. Because it is most preferred 5 that screening take place by use of a mammalian expression system, such a system will be expected to have endogenous G protein therein. Thus, by definition, in such a system, the constitutively activated orphan GPCR will continuously signal. In this regard, it is preferred that this signal be enhanced such that in the presence of, e.g., an inverse agonist to the receptor, it is more likely that it will be able to more readily differentiate, particularly in the 10 context of screening, between the receptor when it is contacted with the inverse agonist.

The GPCR Fusion Protein is intended to enhance the efficacy of G protein coupling with the GPCR. The GPCR Fusion Protein is preferred for screening with a non-endogenous constitutively activated GPCR because such an approach increases the signal that is most preferably utilized in such screening techniques, although the GPCR Fusion 15 Protein can also be (and preferably is) used with an endogenous, constitutively activated GPCR. This is important in facilitating a significant "signal to noise" ratio; such a significant ratio is import preferred for the screening of candidate compounds as disclosed herein.

The construction of a construct useful for expression of a GPCR Fusion Protein is within the purview of those having ordinary skill in the art. Commercially available 20 expression vectors and systems offer a variety of approaches that can fit the particular needs of an investigator. The criteria of importance for such a GPCR Fusion Protein construct is that the GPCR sequence and the G protein sequence both be in-frame (preferably, the sequence for the GPCR is upstream of the G protein sequence) and that the "stop" codon of

the GPCR must be deleted or replaced such that upon expression of the GPCR, the G protein

can also be expressed. The GPCR can be linked directly to the G protein, or there can be

spacer residues between the two (preferably, no more than about 12, although this number

can be readily ascertained by one of ordinary skill in the art). We have a preference (based

5 upon convenience) of use of a spacer in that some restriction sites that are not used will,

effectively, upon expression, become a spacer. Most preferably, the G protein that couples

to the GPCR will have been identified prior to the creation of the GPCR Fusion Protein

construct. Because there are only a few G proteins that have been identified, it is preferred

that a construct comprising the sequence of the G protein (i.e., a universal G protein

10 construct) be available for insertion of an endogenous GPCR sequence therein; this provides

for efficiency in the context of large-scale screening of a variety of different endogenous

Although a preferred use of the human orphan GPCRs disclosed herein may be for

5

E. Other Utility

GPCRs having different sequences.

40

30

35

50

55

45

agonists (preferably for use as pharmaceutical agents), these versions of human GPCRs can also be utilized in research settings. For example, in vitro and in vivo systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and diseased, as well as understanding the role of 20 constitutive activation as it applies to understanding the signaling cascade. The value in human orphan GPCRs is that its utility as a research tool is enhanced in that by determining the location(s) of such receptors within the body, the GPCRs can be used to understand the

role of these receptors in the human body before the endogenous ligand therefor is identified.

10

15

20

25

30

35

40

50

45

55

Other uses of the disclosed receptors will become apparent to those in the art based upon, inter alia, a review of this patent document.

EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, 5 of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor modifications to these sequences while achieving the same or substantially similar results reported below. Unless otherwise indicated below, all nucleic acid sequences for the disclosed endogenous orphan human GPCRs have been sequenced and verified. For 10 purposes of equivalent receptors, those of ordinary skill in the art will readily appreciate that conservative substitutions can be made to the disclosed sequences to obtain a functionally equivalent receptor.

Example 1 ENDOGENOUS HUMAN GPCRS

15

1. Identification of Human GPCRs

Several of the disclosed endogenous human GPCRs were identified based upon a review of the GenBank database information. While searching the database, the following cDNA clones were identified as evidenced below.

	Disclosed	Accession	Complete DNA	Open Reading	Nucleic Acid	Amino
20	Human	Number	Sequence	Frame	SEQ.ID.	Acid
	Orphan		(Base Pairs)	(Base Pairs)	NO.	SEQ.ID.
	GPCRs			•		NO.

		PCT/	PCT/US99/23687				
5							
		hARE-3	AL033379	111,389 bp	1,260 bp	1	2
10		hARE-4	AC006087	226,925 bp	1,119 bp	3	4
		hARE-5	AC006255	127,605 bp	1,104 bp	5	6
15		hRUP3	AL035423	140,094 bp	1,005 bp	7	8
	5	hRUP5	AC005849	169,144 bp	1,413 bp	9	10
20		hRUP6	AC005871	218,807 bp	1,245 bp	11	12
		hRUP7	AC007922	158,858 bp	1,173 bp	13	14

Other disclosed endogenous human GPCRs were identified by conducting a BLAST search of EST database (dbest) using the following EST clones as query sequences. The 10 following EST clones identified were then used as a probe to screen a human genomic library.

		Disclosed	Query	EST Clone/	Open	Nucleic Acid	Amino Acid
		Human	(Sequence)	Accession No.	Reading	SEQ.ID.NO.	SEQ.ID.NO.
35		Orphan		ldentified	Frame		
	15	GPCRs hGPCR27	Mouse	AA775870	(Base Pairs) 1,125 bp	15	16
			GPCR27				
40		hARE-1	TDAG	1689643	999 bp	17	18
		hARE-2	GPCR27	A1090920 68530	1,122 bp	19	20
				AA359504			
45		hPPR1	Bovine	238667	1,053 bp	21	22
			PPR1	H67224			
	20	hG2A	Mouse	See Example 2(a),	1,113 bp	23	24
50			1179426	below			

55

25

		WO 00/3125	58				PCT/US99/23687
5				- 18 -			
		hCHN3	N.A.	EST 36581	1,113 bp	25	26
10		hCHN4	TDAG	(full length) 1184934	1,077 bp	27	28
10		hCHN6	N.A.	AA804531 EST 2134670	1,503 bp	29	30
			• • • • • • • • • • • • • • • • • • • •	(full length)	1,505 ор	29	30
		hCHN8	KIAA0001	EST 764455	1,029 bp	31	32
15	5	hCHN 9	1365839	EST 1541536	1,077 bp	33	34
		hCHN10	Mouse EST	Human 1365839	1,005 bp	35	36
			1365839				
		hRUP4	N.A. = "not ap	AI307658 plicable".	1,296 bp	37	38
20		2.	Full Length	Cloning			
	10	a.	hG2A (Seq.	Id. Nos. 23 & 24)			

Mouse EST clone 1179426 was used to obtain a human genomic clone containing all but three amino acid hG2A coding sequences. The 5'end of this coding sequence was obtained by using 5'RACE™, and the template for PCR was Clontech's Human Spleen Marathon-ready™ cDNA. The disclosed human G2A was amplified by PCR using the G2A 15 cDNA specific primers for the first and second round PCR as shown in SEQ.ID.NO.: 39 and SEQ.ID.NO.:40 as follows:

5'-CTGTGTACAGCAGTTCGCAGAGTG-3' (SEQ.ID.NO.: 39; 1" round PCR)

5'-GAGTGCCAGGCAGAGCAGGTAGAC-3' (SEQ.ID.NO.: 40; second round PCR).

PCR was performed using Advantage™ GC Polymerase Kit (Clontech; manufacturing 20 instructions will be followed), at 94°C for 30 sec followed by 5 cycles of 94°C for 5 sec and 72°C for 4 min; and 30 cycles of 94° for 5 sec and 70° for 4 min. An approximate 1.3 Kb PCR fragment was purified from agarose gel, digested with Hind III and Xba I and cloned into the expression vector pRC/CMV2 (Invitrogen). The cloned-insert was sequenced using the T7 Sequenase™ kit (USB Amersham; manufacturer instructions will be followed) and

10

15

20

25

30

35

40

45

50

55

the sequence was compared with the presented sequence. Expression of the human G2A will be detected by probing an RNA dot blot (Clontech; manufacturer instructions will be followed) with the P^{32} -labeled fragment.

b. hCHN9 (Seq. Id. Nos. 33 & 34)

Sequencing of the EST clone 1541536 indicated that hCHN9 is a partial cDNA clone having only an initiation codon; i.e., the termination codon was missing. When hCHN9 was used to "blast" against the data base (nr), the 3' sequence of hCHN9 was 100% homologous to the 5' untranslated region of the leukotriene B4 receptor cDNA, which contained a termination codon in the frame with hCHN9 coding sequence. To 10 determine whether the 5' untranslated region of LTB4R cDNA was the 3' sequence of hCHN9, PCR was performed using primers based upon the 5' sequence flanking the initiation codon found in hCHN9 and the 3' sequence around the termination codon found in the LTB4R 5' untranslated region. The 5' primer sequence utilized was as follows: 5'-CCCGAATTCCTGCTTGCTCCCAGCTTGGCCC-3' (SEQ.ID.NO.: 41; sense) and 15 5'-TGTGGATCCTGCTGTCAAAGGTCCCATTCCGG-3' (SEQ.ID.NO.: 42; antisense). PCR was performed using thymus cDNA as a template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 65°C for 1 min and 72 °C for 1 min and 10 sec. A 1.1kb fragment consistent with the predicted size was 20 obtained from PCR. This PCR fragment was subcloned into pCMV (see below) and

c. hRUP 4 (Seq. Id. Nos. 37 & 38)

sequenced (see, SEQ.ID.NO.: 33).

The full length hRUP4 was cloned by RT-PCR with human brain cDNA (Clontech)

15

20

25

30

35

40

45

50

as templates:

5'-TCACAATGCTAGGTGTGGTC-3' (SEQ.ID.NO.: 43; sense) and

5'-TGCATAGACAATGGGATTACAG-3' (SEQ.ID.NO.: 44; antisense).

PCR was performed using TaqPlus™ Precision™ polymerase (Stratagene; manufacturing 5 instructions will be followed) by the following cycles: 94°C for 2 min; 94°C 30 sec; 55°C for 30 sec, 72°C for 45 sec, and 72°C for 10 min. Cycles 2 through 4 were repeated 30 times.

The PCR products were separated on a 1% agarose gel and a 500 bp PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and sequenced using the 10 T7 DNA Sequenase™ kit (Amsham) and the SP6/T7 primers (Stratagene). Sequence analysis revealed that the PCR fragment was indeed an alternatively spliced form of AI307658 having a continuous open reading frame with similarity to other GPCRs. The completed sequence of this PCR fragment was as follows:

Based on the above sequence, two sense oligonucleotide primer sets:

5'-CTGCTTAGAAGAGTGGACCAG-3' (SEQ.ID.NO.: 46; oligo 1),

25 5'-CTGTGCACCAGAAGATCTACAC-3' (SEQ.IDNO.: 47; oligo 2)

and two antisense oligonucleotide primer sets:

5'-CAAGGATGAAGGTGGTGTAGA-3' (SEQ.ID.NO.: 48; oligo 3)

5'-GTGTAGATCTTCTGGTGCACAGG-3' (SEQ.ID.NO.: 49; oligo 4)

were used for 3'- and 5'-race PCR with a human brain Marathon-Ready™ cDNA (Clontech,

Cat# 7400-1) as template, according to manufacture's instructions. DNA fragments generated by the RACE PCR were cloned into the pCRII-TOPO™ vector (Invitrogen) and sequenced using the SP6/T7 primers (Stratagene) and some internal primers. The 3' RACE product contained a poly(A) tail and a completed open reading frame ending at a TAA stop 5 codon. The 5' RACE product contained an incomplete 5' end; *i.e.*, the ATG initiation codon was not present.

Based on the new 5' sequence, oligo 3 and the following primer:

5'-GCAATGCAGGTCATAGTGAGC -3' (SEQ.ID.NO.: 50; oligo 5)

were used for the second round of 5' RACE PCR and the PCR products were analyzed as 10 above. A third round of 5' RACE PCR was carried out utilizing antisense primers:

5'-TGGAGCATGGTGACGGGAATGCAGAAG-3' (SEQ.ID.NO.: 51; oligo 6) and

5'-GTGATGAGCAGGTCACTGAGCGCCAAG-3' (SEQ.ID.NO.: 52; oligo7).

The sequence of the 5' RACE PCR products revealed the presence of the initiation codon ATG, and further round of 5' RACE PCR did not generate any more 5' sequence. The 15 completed 5' sequence was confirmed by RT-PCR using sense primer

5'-GCAATGCAGGCGCTTAACATTAC-3' (SEQ.ID.NO.: 53; oligo 8) and oligo 4 as primers and sequence analysis of the 650 bp PCR product generated from human brain and heart cDNA templates (Clontech, Cat# 7404-1). The completed 3' sequence was confirmed by RT-PCR using oligo 2 and the following antisense primer:

20 5'-TTGGGTTACAATCTGAAGGGCA-3' (SEQ.ID.NO.: 54; oligo 9)
and sequence analysis of the 670 bp PCR product generated from human brain and heart
cDNA templates. (Clontech, Cat# 7404-1).

d. hRUP5 (Seq. Id. Nos. 9 & 10)

The full length hRUP5 was cloned by RT-PCR using a sense primer upstream from

35

40

45

5

10

15

20

25

30

35

40

45

50

55

ATG, the initiation codon (SEQ.ID.NO.: 55), and an antisense primer containing TCA as the stop codon (SEQ.ID.NO.: 56), which had the following sequences:

- 5'-ACTCCGTGTCCAGCAGGACTCTG-3' (SEQ.ID.NO.:55)
- 5'-TGCGTGTTCCTGGACCCTCACGTG-3' (SEQ.ID.NO.: 56)
- 5 and human peripheral leukocyte cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech) was used for the amplification in a 50ul reaction by the following cycle with step 2 through step 4 repeated 30 times: 94°C for 30 sec; 94° for 15 sec; 69° for 40 sec; 72°C for 3 min; and 72°C fro 6 min. A 1.4kb PCR fragment was isolated and cloned with the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the T7 DNA 10 Sequenase™ kit (Amsham). See, SEQ.ID.NO.: 9.

e. hRUP6 (Seq. Id. Nos. 11 & 12)

The full length hRUP6 was cloned by RT-PCR using primers:

- 5'-CAGGCCTTGGATTTTAATGTCAGGGATGG-3' (SEQ.ID.NO.: 57) and
- 5'-GGAGAGTCAGCTCTGAAAGAATTCAGG-3' (SEQ.ID.NO.: 58);
- 15 and human thymus Marathon-Ready™ cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech, according to manufacturer's instructions) was used for the amplification in a 50ul reaction by the following cycle: 94°C for 30sec; 94°C for 5 sec; 66°C for 40sec; 72°C for 2.5 sec and 72°C for 7 min. Cycles 2 through 4 were repeated 30 times. A 1.3 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) 20 and completely sequenced (see, SEQ.ID.NO.: 11) using the ABI Big Dye Terminator™ kit (P.E. Biosystem).

f. hRUP7 (Seq. Id. Nos. 13 & 14)

The full length RUP7 was cloned by RT-PCR using primers:

5'-TGATGTGATGCCAGATACTAATAGCAC-3' (SEQ.ID.NO.: 59; sense) and

10

15

20

25

30

35

40

45

50

5'-CCTGATTCATTTAGGTGAGATTGAGAC-3' (SEQ.ID.NO.: 60; antisense)
and human peripheral leukocyte cDNA (Clontech) as a template. Advantage™ cDNA
polymerase (Clontech) was used for the amplification in a 50 ul reaction by the following
cycle with step 2 to step 4 repeated 30 times: 94°C for 2 minutes; 94°C for 15 seconds; 60°C
5 for 20 seconds; 72°C for 2 minutes; 72°C for 10 minutes. A 1.25 Kb PCR fragment was
isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced
using the ABI Big Dye Terminator™ kit (P.E. Biosystem). See, SEQ.ID.NO.: 13.

g. hARE-5 (Seq. Id. Nos. 5 & 6)

The full length hARE-5 was cloned by PCR using the hARE5 specific primers 10 5'-CAGCGCAGGGTGAAGCCTGAGAGC-3' SEQ.ID.NO.: 69 (sense, 5' of initiation codon ATG) and 5'-GGCACCTGCTGTGCAGG-3' SEQ.ID.NO.:70 (antisense, 3' of stop codon TGA) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 96°C, 2 minutes; 96°C, 20 seconds; 58°C, 30 seconds; 72°C, 2 minutes; and 72°C, 10 minutes

A 1.1 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (SEQ.ID.NO.:5) using the T7 DNA Sequenase™ kit (Amsham).

h. hARE-4 (Seq. Id. Nos.: 3 & 4)

The full length hARE-4 was cloned by PCR using the hARE-4 specific primers 5'20 CTGGTGTGCTCCATGGCATCCC-3' SEQ.ID.NO.:67 (sense, 5' of initiation codon ATG) and 5'GTAAGCCTCCCAGAACGAGAGG-3' SEQ.ID.NO.: 68 (antisense, 3' of stop codon TGA) and
human genomic DNA as template. Taq DNA polymerase (Stratagene) and 5% DMSO was
used for the amplification by the following cycle with step 2 to step 3 repeated 35 times:

94°C, 3 minutes; 94°C, 30 seconds; 59°C, 2 minutes; 72°C, 10 minutes

10

A 1.12 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (SEQ.ID.NO.:3) using the T7 DNA Sequenase™ kit (Amsham).

gatcaagcttCCATCCTACTGAAACCATGGTC-3' SEQ.ID.NO.:65 (sense, lower case nucleotides

15

i. hARE-3 (Seq.Id.Nos.: 1 & 2)

20

represent Hind III overhang, ATG as initiation codon) and 5'-

The full length hARE-3 was cloned by PCR using the hARE-3 specific primers 5'-

gatcagatctCAGTTCCAATATTCACACCACCGTC-3' SEQ.ID.NO.:66 (antisense, lower case

25

10 nucleotides represent Xba I overhang, TCA as stop codon) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for the amplification

by the following cycle with step 2 to step 4 repeated 35 times: 94°C, 3 minutes; 94°C, 1

30

minute; 55°C, 1 minute; 72°C, 2 minutes; 72°C, 10 minutes.

35

A 1.3 Kb PCR fragment of predicated size was isolated and digested with Hind III 15 and Xba I, cloned into the pRC/CMV2 vector (Invitrogen) at the Hind III and Xba I sites and completely sequenced (SEQ.ID.NO.:1) using the T7 DNA Sequenase™ kit (Amsham).

j. hRUP3 (Seq. Id. Nos.: 7 & 8)

40

GTCCTGCCACTTCGAGACATGG-3' SEQ.ID.NO.:71 (sense, ATG as initiation codon) and 5'-

The full length hRUP3 was cloned by PCR using the hRUP3 specific primers 5'-

45

20 GAAACTTCTCTGCCCTTACCGTC-3' SEQ.ID.NO.:72 (antisense, 3' of stop codon TAA) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was

used for the amplification by the following cycle with step 2 to step 4 repeated 35 times:

50

94°C, 3 minutes; 94°C, 1 minute; 58°C, 1 minute; 72°C, 2 minutes; 72°C, 10 minutes

10

15

20

30

25

35

40

45

50

A 1.0 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPOTM vector (Invitrogen) and completely sequenced (SEQ.ID.NO.: 7)using the T7 DNA sequenase kit (Amsham).

Example 2 5 RECEPTOR EXPRESSION

Although a variety of cells are available to the art for the expression of proteins, it is most preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, *i.e.*, utilization of, *e.g.*, yeast cells for the expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the 10 case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretary pathways that have evolved for mammalian systems – thus, results obtained in non-mammalian cells, while of potential use, are not as preferred as that obtained from mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular 15 needs of the artisan. The general procedure for expression of the disclosed GPCRs is as follows.

On day one, 1X10⁷ 293T cells per 150mm plate were plated out. On day two, two reaction tubes will be prepared (the proportions to follow for each tube are per plate): tube A will be prepared by mixing 20µg DNA (e.g., pCMV vector; pCMV vector with receptor 20 cDNA, etc.) in 1.2ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B will be prepared by mixing 120µl lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B are admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture can be referred to as the "transfection mixture". Plated 293T cells are washed with 1XPBS, followed by addition of 10ml serum free DMEM.

10

15

20

30

25

35

40

45

50

55

- 26 -

2.4ml of the transfection mixture will then be added to the cells, followed by incubation for 4hrs at 37°C/5% CO₂. The transfection mixture was then be removed by aspiration, followed by the addition of 25ml of DMEM/10% Fetal Bovine Serum. Cells will then be incubated at 37°C/5% CO₂. After 72hr incubation, cells can then be harvested and utilized for analysis.

5 Example 3

TISSUE DISTRIBUTION OF THE DISCLOSED HUMAN GPCRS

Several approaches can be used for determination of the tissue distribution of the GPCRs disclosed herein.

1. Dot-Blot Analysis

Using a commercially available human-tissue dot-blot format, endogenous orphan GPCRs were probed for a determination of the areas where such receptors are localized. cDNA fragments from the GPCRs of Example 1 (radiolabelled) were (or can be) used as the probe: radiolabeled probe was (or can be) generated using the complete receptor cDNA (excised from the vector) using a Prime-It II™ Random Primer Labeling Kit (Stratagene, 15 #300385), according to manufacturer's instructions. A human RNA Master Blot™ (Clontech, #7770-1) was hybridized with the endogenous human GPCR radiolabeled probe and washed under stringent conditions according manufacturer's instructions. The blot was exposed to Kodak BioMax™ Autoradiography film overnight at -80°C. Results are summarized for several receptors in Table B and C (see Figures 1A and 1B for a grid 20 identifying the various tissues and their locations, respectively). Exemplary dot-blots are provided in Figure 2A and 2B for results derived using hCHN3 and hCHN8, respectively.

TABLE B

ORPHAN GPCR

Tissue Distribution (highest levels, relative to other tissues in the dot-blot)

. • • •

P	C	T	π	IS	9	9,	2	3	6	8	7
---	---	---	---	----	---	----	---	---	---	---	---

WO 00/31258	
-------------	--

- 27 -

•	hGPCR27 Fetal brain, Putamen, Pituitary gland. Caudate nucleus			
	hARE-1 Spleen, Peripheral leukocytes. Fetal spleen			
10	hPPR1 Pituitary gland, Heart, salivary gland. Small intestine, Testis			
	hRUP3 Pancreas			
	5 hCHN3 Fetal brain, Putamen, Occipital cortex			
15	hCHN9 Pancreas, Small intestine, Liver			
•	hCHN10 Kidney, Thryoid			
20	TABLE C			
	ORPHAN GPCR Tissue Distribution (highest levels, relative to other tissues in the dot-blot)			
25	10 hARE-3 Cerebellum left, Cerebellum right, Testis, Accumbens			
20	hGPCR3 Corpus collusum, Caudate nucleus, Liver, Heart, Inter- Ventricular Septum			
	hARE-2 Cerebellum left, Cerebellum right, Substantia			
30	hCHN8 Cerebellum left, Cerebellum right, Kidney, Lung			
	2 DT BCD			
35	2. RT-PCR			
	15 a. hRUP3			
	To ascertain the tissue distribution of hRUP3 mRNA, RT-PCR was performed using			
40	hRUP3-specific primers and human multiple tissue cDNA panels (MTC, Clontech) as			
	templates. Taq DNA polymerase (Stratagene) was utilized for the PCR reaction, using the			
	following reaction cycles in a 40ul reaction: 94°C for 2 min; 94°C for 15 sec; 55°C for 30			
45	20 sec; 72°C for 1 min; 72° C, for 10 min. Primers were as follows:			
	5'-GACAGGTACCTTGCCATCAAG-3' (SEQ.ID.NO.: 61; sense)			
	5'-CTGCACAATGCCAGTGATAAGG-3' (SEQ.ID.NO.: 62; antisense).			

50

55

20ul of the reaction was loaded onto a 1% agarose gel; results are set forth in Figure 3.

5

15

20

25

30

35

40

45

50

55

As is supported by the data of Figure 3, of the 16 human tissues in the cDNA panel utilized (brain, colon, heart, kidney, lung, ovary, pancreas, placenta, prostate, skeleton, small intestine, spleen, testis, thymus leukocyte, and liver) a single hRUP3 band is evident only from the pancreas. Additional comparative analysis of the protein sequence of hRUP3 with 5 other GPCRs suggest that hRUP3 is related to GPCRs having small molecule endogenous ligand such that it is predicted that the endogenous ligand for hRUP3 is a small molecule.

b. hRUP4

RT-PCR was performed using hRUP4 oligo's 8 and 4 as primers and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase 10 (Stratagene) was used for the amplification in a 40ul reaction by the following cycles: 94°C for 30 seconds, 94°C for 10 seconds, 55°C for 30 seconds, 72°C for 2 minutes, and 72°C for 5 minutes with cycles 2 through 4 repeated 30 times.

20 µl of the reaction were loaded on a 1% agarose gel to analyze the RT-PCR products, and hRUP4 mRNA was found expressed in many human tissues, with the strongest 15 expression in heart and kidney. (see, Figure 4). To confirm the authenticity of the PCR fragments, a 300 bp fragment derived from the 5' end of hRUP4 was used as a probe for the Southern Blot analysis. The probe was labeled with ⁵²P-dCTP using the Prime-It II™ Random Primer Labeling Kit (Stratagene) and purified using the ProbeQuant™ G-50 micro columns (Amersham). Hybridization was done overnight at 42° C following a 12 hr pre-20 hybridization. The blot was finally washed at 65°C with 0.1 x SSC. The Southern blot did confirm the PCR fragments as hRÚP4.

c. hRUP5

RT-PCR was performed using the following hRUP5 specific primers:

5

10

15

20

25

30

35

40

45

50

5'-CTGACTTCTTGTTCCTGGCAGCAGCGG-3' (SEQ.ID.NO.: 63; sense)
5'-AGACCAGCCAGGCACGCTGAAGAGTG-3' (SEQ.ID.NO.: 64; antisense)
and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA
5 polymerase (Stratagene) was used for the amplification in a 40ul reaction by the following cycles: 94°C for 30 sec, 94°C for 10 sec, 62°C for 1.5 min, 72°C for 5 min, and with cycles
2 through 3 repeated 30 times. 20 μl of the reaction were loaded on a 1.5% agarose gel to analyze the RT-PCR products, and hRUP5 mRNA was found expressed only in the peripheral blood leukocytes (*data not shown*).

10 d. hRUP6

RT-PCR was applied to confirm the expression and to determine the tissue distribution of hRUP6. Oligonucleotides used, based on an alignment of AC005871 and GPR66 segments, had the following sequences:

5'-CCAACACCAGCATCCATGGCATCAAG-3' (SEQ.ID.NO.: 73; sense),

15 5'-GGAGAGTCAGCTCTGAAAGAATTCAGG-3' (SEQ.ID.NO.: 74; antisense)
and the human multiple tissue cDNA panels (MTC, Clontech) were used as templates.

PCR was performed using TaqPlus Precision™ polymerase (Stratagene; manufacturing instructions will be followed) in a 40ul reaction by the following cycles: 94°C for 30 sec; 94°C 5 sec; 66°C for 40 sec, 72°C for 2.5 min, and 72°C for 7 min. Cycles 2 through 4 20 were repeated 30 times.

20 ul of the reaction were loaded on a 1.2% agarose gel to analyze the RT-PCR products, and a specific 760bp DNA fragment representing hRUP6 was expressed predominantly in the thymus and with less expression in the heart, kidney, lung, prostate small intestine and testis. (see, Figure 5).

- 30 -

It is intended that each of the patents, applications, and printed publications mentioned in this patent document be hereby incorporated by reference in their entirety.

As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the 5 spirit of the invention. It is intended that all such variations fall within the scope of the invention and the claims that follow.

Although a variety of Vectors are available to those in the art, for purposes of utilization for both endogenous and non-endogenous human GPCRs, it is most preferred that the Vector utilized be pCMV. This vector was deposited with the American Type 10 Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

Claims

THIS PAGE BLANK (USPTO)

• • •

wo	OO.	31	258

PCT/US99/23687

	31		
--	----	--	--

CLAIMS	CL	A	II	И	S
---------------	----	---	----	---	---

10	
	What is claimed is

5

15

20

25

30

35

40

45

50

- 1. A cDNA encoding a human G protein-coupled receptor comprising SEQ.ID.NO.: 1.
- 5 2. A human G protein-coupled receptor encoded by the cDNA of SEQ.ID.NO.: 1 comprising SEQ.ID.NO.: 2.
 - 3. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:1.
 - 4. A Host Cell comprising the Plasmid of claim 3.
- 5. A cDNA encoding a human G protein-coupled receptor comprising 10 SEQ.ID.NO.: 3.
 - 6. A human G protein-coupled receptor encoded by the cDNA of SEQ.ID.NO.: 3 comprising SEQ.ID.NO.: 4.
 - 7. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:3.
 - 8. A Host Cell comprising the Plasmid of claim 7.
- 9. A cDNA encoding a human G protein-coupled receptor comprising SEQ.ID.NO.: 5.
 - 10. A human G protein-coupled receptor encoded by the cDNA of SEQ.ID.NO.: 5 comprising SEQ.ID.NO.: 6.
 - 11. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:5.
- 20 12. A Host Cell comprising the Plasmid of claim 11.
 - 13. A cDNA encoding a human G protein-coupled receptor comprising SEQ.ID.NO.: 7.

5			- 32 -
		14.	A human G protein-coupled receptor encoded by the cDNA of
	SEQ	.ID.NO	: 7 comprising SEQ.ID.NO.: 8.
10		15.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:7.
		16.	A Host Cell comprising the Plasmid of claim 15.
15	5	17.	A cDNA encoding a human G protein-coupled receptor comprising
	SEQ	.ID.NO	: 9.
		18.	A human G protein-coupled receptor encoded by the cDNA of
20	SEQ	.ID.NO.	: 9 comprising SEQ.ID.NO.: 10.
		19.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:9.
25	10	20.	A Host Cell comprising the Plasmid of claim 19.
20		21.	A cDNA encoding a human G protein-coupled receptor comprising
	SEQ	.ID.NO.	: 11.
30		22.	A human G protein-coupled receptor encoded by the cDNA of
	SEQ.	ID.NO.	: 11 comprising SEQ.ID.NO.:12.
	15	23.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:11.
35		24.	A Host Cell comprising the Plasmid of claim 23.
		25.	A cDNA encoding a human G protein-coupled receptor comprising
40	SEQ.	ID.NO.	13.
		26.	A human G protein-coupled receptor encoded by the cDNA of
	20 SEQ.	ID.NO.:	13 comprising SEQ.ID.NO.: 14.
45		27.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:13.
		28.	A Host Cell comprising the Plasmid of claim 27.
50		29.	A cDNA encoding a human G protein-coupled receptor comprising

44.

5			- 33 -
	SEC	Q.ID.NO	.: 15.
		30.	A human G protein-coupled receptor encoded by the cDNA of
10	SEC	ON.DI.Q	.: 15 comprising SEQ.ID.NO.: 16.
		31.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:15.
15	5	32.	A Host Cell comprising the Plasmid of claim 31.
		33.	A cDNA encoding a human G protein-coupled receptor comprising
	SEC	ON.DI.	: 17.
20		34.	A human G protein-coupled receptor encoded by the cDNA of
	SEC	ON.DI.	: 17 comprising SEQ.ID.NO.: 18.
	10	35.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:17.
25		36.	A Host Cell comprising the Plasmid of claim 35.
		37.	A cDNA encoding a human G protein-coupled receptor comprising
30	SEC	.ID.NO.	: 19.
		38.	A human G protein-coupled receptor encoded by the cDNA of
	15 SEQ	.ID.NO.	: 19 comprising SEQ.ID.NO.: 20.
35		39 .	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:19.
		40.	A Host Cell comprising the Plasmid of claim 39.
40		41.	A cDNA encoding a human G protein-coupled receptor comprising
	SEQ	.ID.NO.	: 21.
	20	42.	A human G protein-coupled receptor encoded by the cDNA of
45	SEQ	.ID.NO.	: 21 comprising SEQ.ID.NO.: 22.
		43	A Plasmid comprising a Vector and the cDNA of SEO ID NO. 21

A Host Cell comprising the Plasmid of claim 43.

5			- 34 -
		45.	A cDNA encoding a human G protein-coupled receptor comprising
•	SEC	Q.ID.NO	.: 23.
10		46.	A human G protein-coupled receptor encoded by the cDNA of
	SEC	Q.ID.NO	.: 23 comprising SEQ.ID.NO.: 24.
15	. 5	47.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.: 23.
		48.	A Host Cell comprising the Plasmid of claim 47.
		49.	A cDNA encoding a human G protein-coupled receptor comprising
20	SEC	ON.DI.	: 25.
		50.	A human G protein-coupled receptor encoded by the cDNA of
25	10 SEQ	ON.DI.	: 25 comprising SEQ.ID.NO.: 26.
25		51.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:25.
		52.	A Host Cell comprising the Plasmid of claim 51.
30		53.	A cDNA encoding a human G protein-coupled receptor comprising
	SEQ	.ID.NO.	: 27.
	15	54.	A human G protein-coupled receptor encoded by the cDNA of
35	SEQ	.ID.NO.	: 27 comprising SEQ.ID.NO.: 28.
		55.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:27.
40		56.	A Host Cell comprising the Plasmid of claim 55.
		57.	A cDNA encoding a human G protein-coupled receptor comprising
	20 SEQ	.ID.NO.:	29.
45		58.	A human G protein-coupled receptor encoded by the cDNA of
	SEQ	.ID.NO.:	29 comprising SEQ.ID.NO.: 30.
50		59 .	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:29.

•			55
		60.	A Host Cell comprising the Plasmid of claim 59.
		61.	A cDNA encoding a human G protein-coupled receptor comprising
10	SE	Q.ID.NO	D.: 31.
		62.	A human G protein-coupled receptor encoded by the cDNA of
15	5 SEC	Q.ID.NO	.: 31 comprising SEQ.ID.NO.: 32.
		63.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:31
		64.	A Host Cell comprising the Plasmid of claim 63.
20		6 5.	A cDNA encoding a human G protein-coupled receptor comprising
	SEC	Q.ID.NO	.: 33.
0.5	10	66.	A human G protein-coupled receptor encoded by the cDNA of
25	SEC	ON.DI.	.: 33 comprising SEQ.ID,NO.: 34.
		67.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:33
30		68.	A Host Cell comprising the Plasmid of claim 67.
		69.	A cDNA encoding a human G protein-coupled receptor comprising
	15 SEC	ON.DI.	.: 35.
35		70.	A human G protein-coupled receptor encoded by the cDNA of
	SEQ	.ID.NO.	: 35 comprising SEQ.ID.NO.: 36.
40		71.	A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:35.
		72 .	A Host Cell comprising the Plasmid of claim 71.
	20	7 3.	A cDNA encoding a human G protein-coupled receptor comprising
45	SEQ	.ID.NO.	: 37.
		74.	A human G protein-coupled receptor encoded by the cDNA of
50	SEQ	.ID.NO.	: 37 comprising SEQ.ID.NO.: 38.

5 - 36 -

75. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:37.

76. A Host Cell comprising the Plasmid of claim 75.

	1	2	3	4	5	9	7	8
<		Amygdala		Caudate Cerebellum	Cerabral	Frontal	Hippocampus Medulla	Medulla
-		·	Nucleus		Cortex	Cortex		Oblongata
В	Occipital	Putamen	Substantia	Temporal	Thalamus	Accumbens	Thalamus Accumbens Spinal Cord	
	Cortex		Nigra	Cortex				
ິ ວ	Heart	Aorta	Skeletal	Colon	Bladder	Uterus	Prostate	Stomach
			Muscle					
Ω	Testis	Ovary	Pancreas	Pituitary	Adrenal	Thyroid	Salivary	Mammary
					Gland		Gland	Gland
山	Kidney	Liver	Small	Spleen	Thymus	Peripheral	Lymph	Вопе
			Intestine			Leukocyte	Node	Магтом
ഥ	Appendix	Lung	Trachea	Placenta				
G	Fetal	Fetal	Fetal	Fetal	Fetal	Fetal	Fetal	
	Brain	Heart	Kidney	Liver	Spleen	Thymus	Lung	
Н								

SUBSTITUTE SHEET (RULE 26)

FIG. 1A

	-	-										2/	4							.,
12			I		I							Ĺ			Ι		*	Т		
=	Fetal	Brain	Fetal	Heart	Feta	Kidney	Fetal	Liver	Fetal	Spleen		Fetal	Thymas		Fetal	L)			'
01	Lœukemia	HI_60	Hel a S3		Leukemia	K562	Leukemia	MOLT-4	Burkitt's	Lymphoma	Raii	Burkitt's	Lymphoma	Daudi	Colorectal	Adenocarcinoma	SW480	Juno	Carcinoma	A549
6	Liver		Pancreas		Adrenal		Thyroid		Salivary	_		Mammary	Gland							
∞	Lung		Placenta		Bladder		Uterius		Prostate			Testis		-	Ovary	•				
7	Kidney		Skeletal	Muscle	Spleen		Thymas		Peripheral	Leukocyte		Lymph	Node		Bone	Marrow		Trachea		
9	Colon	Transverse	Color	Desending	Rectum														_	_
5	Esophagus		Storrach		Duodenum		Jejunum		lleum			llocecum			Appendix			Colon	Ascending	
4	Heart		Aorta		Atrium	Left	Atrium	Right	Ventricle	Left		Ventricle	Right		Inter	Ventricular	Septum	Apex of	the Heart	
3	Substantia	Nigra	Accumbens		Thalamus		Pituitary	Gland	Spinal	Cord										
2	Carebellum	left	Cerebellum	Right	Corpus	Callosum	Amygdala		Claudete	Nucleus		Hippocampus			Mechulla	Oblongata		Putamen		
-			Cerebral	Cortex	Frontal	Cortex	Parietal	Lobe	Occipital	Cortex		Temporal	Cortex		Paracentral	Gyrus of	Cerebral	Pons		

SUBSTITUTE SHEET (RULE 26)

FIG. 108

BEST AVAILABLE COPY

WO 00/31258 PCT/US99/23687

3/4

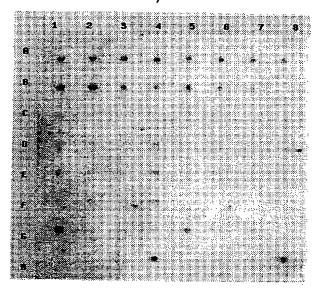
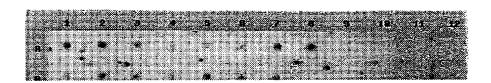
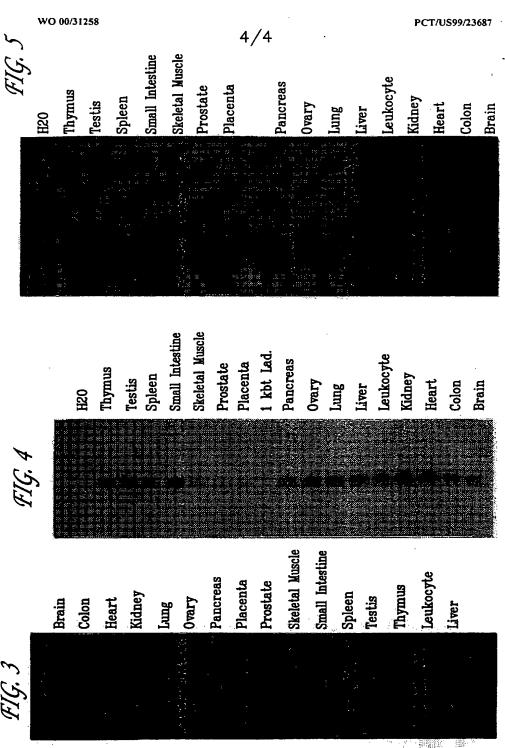


FIG. 2A



BEST AVAILABLE COPY



SUBSTITUTE SHEET (RULE 26)

WO 00/31258

SEQUENCE LISTING

	(1) GENE	RAL INFORMATION:
	(i)	APPLICANT: Chen, Ruoping
	\-/	Dang, Huong T.
5		Liaw, Chen W.
		Lin, I-Lin
÷.	(ii)	TITLE OF INVENTION: Human Orphan G Protein-Coupled Receptors
10	(iii)	NUMBER OF SEQUENCES: 74
10	(iv)	CORRESPONDENCE ADDRESS:
• ; •		(A) ADDRESSEE: Arena Pharmaceuticals, Inc.
•		(B) STREET: 6166 Nancy Ridge Drive
		(C) CITY: San Diego
٠,		(D) STATE: CA
15		(E) COUNTRY: USA
:		(F) ZIP: 92121
	()	COMPUTED DESIDED TO THE
	(V)	COMPUTER READABLE FORM:
		(A) MEDIUM TYPE: Floppy disk
20		(B) COMPUTER: IBM PC compatible (C) OPERATING SYSTEM: PC-DOS/MS-DOS
20		
		(D) SOFTWARE: PatentIn Release #1.0, Version #1.30
	(vi)	CURRENT APPLICATION DATA:
		(A) APPLICATION NUMBER: US
		(B) FILING DATE:
25		(C) CLASSIFICATION:
:		
	(viii)	ATTORNEY/AGENT INFORMATION:
		(A) NAME: Burgoon, Richard P.
¥ -		(B) REGISTRATION NUMBER: 34,787
	(ix)	TELECOMMUNICATION INFORMATION:
30		(A) TELEPHONE: (858)453-7200
		(B) TELEFAX: (858)453-7210
. (2) INFO	RMATION FOR SEQ ID NO:1:
·	_,	
	(i)	SEQUENCE CHARACTERISTICS:
		(A) LENGTH: 1260 base pairs
35		(B) TYPE: nucleic acid
		(C) STRANDEDNESS: single
		(D) TOPOLOGY: linear
	(i:	i) MOLECULE TYPE: DNA (genomic)
	/	CECUIPACE DESCRIPTION, CRO. TD. NO. 1
	(X	i) SEQUENCE DESCRIPTION: SEQ ID NO:1:
		·

40 ATGGTCTTCT CGGCAGTGTT GACTGCGTTC CATACCGGGA CATCCAACAC AACATTTGTC 60

• •

-2-

GTGTATGAAA ACACCTACAT GAATATTACA CTCCCTCCAC CATTCCAGCA TCCTGACCTC 120 AGTCCATTGC TTAGATATAG TTTTGAAACC ATGGCTCCCA CTGGTTTGAG TTCCTTGACC 180 GTGAATAGTA CAGCTGTGCC CACAACACCA GCAGCATTTA AGAGCCTAAA CTTGCCTCTT 240 CAGATCACCC TTTCTGCTAT AATGATATTC ATTCTGTTTG TGTCTTTTCT TGGGAACTTG 300 5 GTTGTTTGCC TCATGGTTTA CCAAAAAGCT GCCATGAGGT CTGCAATTAA CATCCTCCTT 360 GCCAGCCTAG CTTTTGCAGA CATGTTGCTT GCAGTGCTGA ACATGCCCTT TGCCCTGGTA 420 ACTATTCTTA CTACCCGATG GATTTTTGGG AAATTCTTCT GTAGGGTATC TGCTATGTTT 480 TTCTGGTTAT TTGTGATAGA AGGAGTAGCC ATCCTGCTCA TCATTAGCAT AGATAGGTTC 540 CTTATTATAG TCCAGAGGCA GGATAAGCTA AACCCATATA GAGCTAAGGT TCTGATTGCA 600 10 GTTTCTTGGG CAACTTCCTT TTGTGTAGCT TTTCCTTTAG CCGTAGGAAA CCCCGACCTG 660 CAGATACCTT CCCGAGCTCC CCAGTGTGTG TTTGGGTACA CAACCAATCC AGGCTACCAG 720 GCTTATGTGA TTTTGATTTC TCTCATTTCT TTCTTCATAC CCTTCCTGGT AATACTGTAC 780 TCATTTATGG GCATACTCAA CACCCTTCGG CACAATGCCT TGAGGATCCA TAGCTACCCT 840 GAAGGTATAT GCCTCAGCCA GGCCAGCAAA CTGGGTCTCA TGAGTCTGCA GAGACCTTTC 900 15 CAGATGAGCA TTGACATGGG CTTTAAAACA CGTGCCTTCA CCACTATTTT GATTCTCTTT 960 GCTGTCTTCA TTGTCTGCTG GGCCCCATTC ACCACTTACA GCCTTGTGGC AACATTCAGT1020 AAGCACTTTT ACTATCAGCA CAACTTTTTT GAGATTAGCA CCTGGCTACT GTGGCTCTGC1080 TACCTCAAGT CTGCATTGAA TCCGCTGATC TACTACTGGA GGATTAAGAA ATTCCATGAT1140 20 GCTTGCCTGG ACATGATGCC TAAGTCCTTC AAGTTTTTGC CGCAGCTCCC TGGTCACACA1200 AAGCGACGGA TACGTCCTAG TGCTGTCTAT GTGTGTGGGG AACATCGGAC GGTGGTGTGA1260

(3) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 419 amino acids
- 25 (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:
- 30 Met Val Phe Ser Ala Val Leu Thr Ala Phe His Thr Gly Thr Ser Asn 1 5 10 15

- 3 -

	Thr	Thr	Phe	Val 20	Val	Tyr	Glu	Asn	Thr 25	Tyr	Met	Asn	Ile	Thr 30	Leu	Pro
	Pro	Pro	Phe 35	Gln	His	Pro	Asp	Leu 40	Ser	Pro	Leu	Leu	Arg 45	Tyr	Ser	Phe
5	Glu	Thr 50	Met	Ala	Pro	Thr	Gly 55	Leu	Ser	Ser	Leu	Thr 60	Val	Asn	Ser	Thr
	Ala 65	Val	Pro	Thr	Thr	Pro 70	Ala	Ala	Phe	Lys	Ser 75	Leu	Asn	Leu	Pro	Leu 80
10	Gln	Ile	Thr	Leu	Ser 85	Ala	Ile	Met	Ile	Phe 90	Ile	Leu	Phe	Val	Ser 95	Phe
	Leu	Gly	Asn	Leu 100	Val	Val	Cys	Leu	Met 105	Val	Tyr	Gln	Lys	Ala 110	Ala	Met
	Arg	Ser	Ala 115	Ile	Asn	Ile	Leu	Leu 120	Ala	Ser	Leu	Ala	Phe 125	Ala	Asp	Met
15	Leu	Leu 130	Ala	Val	Leu	Asn	Met 135	Pro	Phe	Ala	Leu	Val 140	Thr	Ile	Leu	Thr
	Thr 145	Arg	Trp	Ile	Phe	Gly 150	Lys	Phe	Phe	Суз	Arg 155	Val	Ser	Ala	Met	Phe 160
20	Phe	Trp	Leu	Phe	Val 165	Ile	Glu	Gly	Val	Ala 170	Ile	Leu	Leu	Ile	Ile 175	Ser
	Ile	Asp	Arg	Phe 180	Leu	Ile	Ile	Val	Gln 185	Arg	Gln	Asp	Lys	Leu 190	Asn	Pro
	Tyr	Arg	Ala 195	Lys	Val	Leu	Ile	Ala 200	Val	Ser	Trp	Ala	Thr 205	Ser	Phe	Cys
25	Val	Ala 210	Phe	Pro	Leu	Ala	Val 215	Gly	Asn	Pro	Asp	Leu 220	Gln	Ile	Pro	Ser
	Arg 225	Ala	Pro	Gln	Cys	Val 230	Phe	Gly	Tyr	Thr	Thr 235	Asn	Pro	Gly	Tyr	Gln 240
30	Ala	Tyr	Val	Ile	Leu 245	Ile	Ser	Leu	Ile	Ser 250	Phe	Phe	Ile	Pro	Phe 255	Leu
	Val	Ile	Leu	Tyr 260	Ser	Phe	Met	Gly	Ile 265	Leu	Asn	Thr	Leu	A rg 270	His	Asn
	Ala	Leu	Arg 275	Ile	His	Ser	Tyr	Pro 280	Glu	Gly	Ile	Cys	Leu 285	Ser	Gln	Ala
35	Ser	Lys 290	Leu	Gly	Leu	Met	Ser 295	Leu	Gln	Arg	Pro	Phe 300	Gln	Met	Ser	Ile
	Asp	Met	Gly	Phe	Lys	Thr	Arg	Ala	Phe	Thr	Thr	Ile	Leu	Ile	Leu	Phe

-4 -

305 310 315 320

Ala Val Phe Ile Val Sys Trp Ala Pro Phe Thr Thr Tyr Ser Leu Val 335

Ala Thr Phe Ser Lys His Phe Tyr Tyr Gln His Asn Phe Phe Glu Ile 350

Ser Thr Trp Leu Leu Trp Leu Cys Tyr Leu Lys Ser Ala Leu Asn Pro 365

Leu Ile Tyr Tyr Trp Arg Ile Lys Lys Phe His Asp Ala Cys Leu Asp 370

Met Met Pro Lys Ser Phe Lys Phe Leu Pro Gln Leu Pro Gly His Thr 400

Lys Arg Arg Ile Arg Pro Ser Ala Val Tyr Val Cys Gly Glu His Arg 415

Thr Val Val

15

20

- (4) INFORMATION FOR SEQ ID NO:3:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1119 base pairs
 - (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATGTTAGCCA ACAGCTCCTC AACCAACAGT TCTGTTCTCC CGTGTCCTGA CTACCGACCT 60

25 ACCCACCGCC TGCACTTGGT GGTCTACAGC TTGGTGCTGG CTGCCGGGCT CCCCCTCAAC 120

GCGCTAGCCC TCTGGGTCTT CCTGCGCGCG CTGCGCGTGC ACTCGGTGGT GAGCGTGTAC 180

ATGTGTAACC TGGCGGCAG CGACCTGCTC TTCACCCTCT CGCTGCCCGT TCGTCTCTCC 240

TACTACGCAC TGCACCACTG GCCCTTCCCC GACCTCCTGT GCCAGACGAC GGGCGCCATC 300

TTCCAGATGA ACATGTACGG CAGCTGCATC TTCCTGATGC TCATCAACGT GGACCGCTAC 360

30 GCCGCCATCG TGCACCCGCT GCGACTGCGC CACCTGCGGC GGCCCGCGT GGCGCGGCTG 420

CTCTGCCTGG GCGTGTGGC GCTCATCCTG GTGTTTGCCG TGCCCGCCG CCGCGTGCAC 480

AGGCCCTCGC GTTGCCGCTA CCGGGACCTC GAGGTGCGC TATGCTTCGA GAGCTTCAGC 540

GACGAGCTGT GGAAAGGCAG GCTGCTGCCC CTCGTGCTGC TGGCCGAGGC GCTGGGCTTC 600

CTGCTGCCCC TGGCGGGGT GGTCTACTCG TCGGGCCGAG TCTTCTGGAC GCTGGCGGCG 660

CCCGACGCCA CGCAGAGCCA GCGGCGGCGG AAGACCGTGC GCCTCCTGCT GGCTAACCTC 720

GTCATCTTCC TGCTGTGCTT CGTGCCCTAC AACAGCACGC TGGCGGTCTA CGGGCTGCTG 780

CGGAGCAAGC TGGTGGCGGC CAGCGTGCCT GCCCGCGATC GCGTGCCGG GGTGCTGATG 840

5 GTGATGGTGC TGCTGGCCGG CGCCAACTGC GTGCTGGACC CGCTGGTGTA CTACTTTAGC 900

GCCGACGAGGCT TCCGCAACAC CCTGCGCGGC CTGGGCACTC CGCACCGGGC CAGCACCTCG 960

GCCACCAACG GGACGCGGG GGCGCTCGCG CAATCCGAAA GGTCCGCCGT CACCACCGAC1020

GCCACCAGGC CGGATGCCG CAGTCAGGGG CTGCTCCGAC CCTCCGACTC CCACTCTCTG1080

TCTTCCTTCA CACAGTGTCC CCAGGGATTCC GCCCTCTGA T1119

10 (5) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 372 amino acids
 - (B) TYPE: amino acid
- (C) STRANDEDNESS:
- 15 (D) TOPOLOGY: not relevant
 - (ii) MOLECULE TYPE: protein
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Leu Ala Asn Ser Ser Ser Thr Asn Ser Ser Val Leu Pro Cys Pro 1 5 10 15

20 Asp Tyr Arg Pro Thr His Arg Leu His Leu Val Val Tyr Ser Leu Val 20 25 30

Leu Ala Ala Gly Leu Pro Leu Asn Ala Leu Ala Leu Trp Val Phe Leu 35 40 45

Arg Ala Leu Arg Val His Ser Val Val Ser Val Tyr Met Cys Asn Leu 50 50 55 60

Ala Ala Ser Asp Leu Leu Phe Thr Leu Ser Leu Pro Val Arg Leu Ser 65 70 75 80

Tyr Tyr Ala Leu His His Trp Pro Phe Pro Asp Leu Leu Cys Gln Thr 85 90 95

Thr Gly Ala Ile Phe Gln Met Asn Met Tyr Gly Ser Cys Ile Phe Leu
100 105 110

Met Leu Ile Asn Val Asp Arg Tyr Ala Ala Ile Val His Pro Leu Arg

- 6 -

	_			_	_	_										
	Leu	130	His	Leu	Arg	Arg	Pro 135	Arg	Val	Ala	Arg	Leu 140		Cys	Leu	Gly
	Val 145	Trp	Ala	Leu	Ile	Leu 150	Val	Phe	Ala	Val	Pro 155	Ala	Ala	Arg	Val	His 160
5	Arg	Pro	Ser	Arg	Сув 165	Arg	Tyr	Arg	Asp	Leu 170	Glu	Val	Arg	Leu	Cys 175	Phe
	Glu	Ser	Phe	Ser 180	Asp	Glu	Leu	Trp	Lys 185	Gly	Arg	Leu	Leu	Pro 190	Leu	Val
10	Leu	Leu	Ala 195	Glu	Ala	Leu	Gly	Phe 200	Leu	Leu	Pro	Leu	Ala 205	Ala	Val	Val
	Tyr	Ser 210	Ser	Gly	Arg	Val	Phe 215	Trp	Thr	Leu	Ala	Arg 220	Pro	Asp	Ala	Thr
	Gln 225	Ser	Gln	Arg	Arg	Arg 230	Lys	Thr	Val	Arg	Leu 235	Leu	Leu	Ala	Asn	Leu 240
15	Val	Ile	Phe	Leu	Leu 245	Сув	Phe	Val	Pro	Tyr 250	Asn	Ser	Thr	Leu	Ala 255	Val
	Tyr	Gly	Leu	Leu 260	Arg	Ser	Lys	Leu	Val 265	Ala	Ala	Ser	Val	Pro 270	Ala	Arg
20	Asp	Arg	Val 275	Arg	Gly	Val	Leu	Met 280	Val	Met	Val	Leu	Leu 285	Ala	Gly	Ala
	' Asn	Сув 290	Val	Leu	Asp	Pro	Leu 295	Val	Tyr	Tyr	Phe	Ser 300	Ala	Glu	Gly	Phe
	Arg 305	Asn	Thr	Leu	Arg	Gly 310	Leu	Gly	Thr	Pro	His 315	Arg	Ala	Arg	Thr	Ser 320
25	Ala	Thr	Asn	Gly	Thr 325	Arg _.	Ala	Ala	Leu	Ala 330	Gln	Ser	Glu	Arg	Ser 335	Ala
	Val	Thr	Thr	Asp 340	Ala	Thr	Arg	Pro	Asp 345	Ala	Ala	Ser	Gln	Gly 350	Leu	Leu
30	Arg	Pro	Ser 355	Asp	Ser	His	Ser	Leu 360	Ser	Ser	Phe	Thr	Gln 365	Cys	Pro	Gln
	Asp	Ser 370	Ala	Leu												

- (6) INFORMATION FOR SEQ ID NO:5:
 - (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1107 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

- 7 -

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5: ATGGCCAACT CCACAGGGCT GAACGCCTCA GAAGTCGCAG GCTCGTTGGG GTTGATCCTG 60 GCAGCTGTCG TGGAGGTGGG GGCACTGCTG GGCAACGGCG CGCTGCTGGT CGTGGTGCTG 120 5 CGCACGCCGG GACTGCGCGA CGCGCTCTAC CTGGCGCACC TGTGCGTCGT GGACCTGCTG 180 GCGGCCGCCT CCATCATGCC GCTGGGCCTG CTGGCCGCAC CGCCGCCCGG GCTGGGCCGC 240 GTGCGCCTGG GCCCGCGCC ATGCCGCGC GCTCGCTTCC TCTCCGCCGC TCTGCTGCCG 300 GCCTGCACGC TCGGGGTGGC CGCACTTGGC CTGGCACGCT ACCGCCTCAT CGTGCACCCG 360 CTGCGGCCAG GCTCGCGGCC GCCGCCTGTG CTCGTGCTCA CCGCCGTGTG GGCCGCGGCG 420 10 GGACTGCTGG GCGCGCTCTC CCTGCTCGGC CCGCCGCCCC CACCGCCCCC TGCTCCTGCT 480 CGCTGCTCGG TCCTGGCTGG GGGCCTCGGG CCCTTCCGGC CGCTCTGGGC CCTGCTGGCC 540 TTCGCGCTGC CCGCCCTCCT GCTGCTCGGC GCCTACGGCG GCATCTTCGT GGTGGCGCGT 600 CGCGCTGCCC TGAGGCCCCC ACGGCCGGCG CGCGGGTCCC GACTCCGCTC GGACTCTCTG 660 GATAGCCGCC TTTCCATCTT GCCGCCGCTC CGGCCTCGCC TGCCCGGGGG CAAGGCGGCC 720 15 CTGGCCCCAG CGCTGGCCGT GGGCCAATTT GCAGCCTGCT GGCTGCCTTA TGGCTGCGCG 780 TGCCTGGCGC CCGCAGCGCG GGCCGCGGAA GCCGAAGCGG CTGTCACCTG GGTCGCCTAC 840 TCGGCCTTCG CGGCTCACCC CTTCCTGTAC GGGCTGCTGC AGCGCCCCGT GCGCTTGGCA 900 CTGGGCCGCC TCTCTCGCCG TGCACTGCCT GGACCTGTGC GGGCCTGCAC TCCGCAAGCC 960 TGGCACCCGC GGGCACTCTT GCAATGCCTC CAGAGACCCC CAGAGGGCCC TGCCGTAGGC1020 20 CCTTCTGAGG CTCCAGAACA GACCCCCGAG TTGGCAGGAG GGCGGAGCCC CGCATACCAG1080 GGGCCACCTG AGAGTTCTCT CTCCTGA

- (7) INFORMATION FOR SEQ ID NO:6:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 368 amino acids
- (B) TYPE: amino acid

- (C) STRANDEDNESS:
- (D) TOPOLOGY: not relevant
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

	Met 1	Ala	Asn	Ser	Thr 5	Gly	Leu	Asn	Ala	Ser 10	Glu	Val	Ala	Gly	Ser 15	Leu
	Gly	Leu	Ile	Leu 20	Ala	Ala	Val	Val	Glu 25	Val	Gly	Ala	Leu	Leu 30	Gly	Asn
5	Gly	Ala	Leu 35	Leu	Val	Val	Val	Leu 40	Arg	Thr	Pro	Gly	Leu 45	Arg	Asp	Ala
	Leu	Tyr 50	Leu	Ala	His	Leu	Сув 55	Val	Val	Asp	Leu	Leu 60	Ala	Ala	Ala	Ser
10	Ile 65	Met	Pro	Leu	Gly	Leu 70	Leu	Ala	Ala	Pro	Pro 75	Pro	Gly	Leu	Gly	Arg 80
	Val	Arg	Leu	Gly	Pro 85	Ala	Pro	Cys	Arg	Ala 90	Ala	Arg	Phe	Leu	Ser 95	Ala
	Ala	Leu	Leu	Pro 100	Ala	Cys	Thr	Leu	Gly 105	Val	Ala	Ala	Leu	Gly 110	Leu	Ala
15	Arg	Tyr	Arg 115	Leu	Ile	Val	His	Pro 120	Leu	Arg	Pro	Gly	Ser 125	Arg	Pro	Pro
	Pro	Val 130	Leu	Val	Leu	Thr	Ala 135	Val	Trp	Ala	Ala	Ala 140	Gly	Leu	Leu	Gly
20	Ala 145	Leu	Ser	Leu	Leu	Gly 150	Pro	Pro	Pro	Ala	Pro 155	Pro	Pro	Ala	Pro	Ala 160
	Arg	Сув	Ser	Val	Leu 165	Ala	Gly	Gly	Leu	Gly 170	Pro	Phe	Arg	Pro	Leu 175	Trp
	Ala	Leu	Leu	Ala 180	Phe	Ala	Leu	Pro	Ala 185	Leu	Leu	Leu	Leu	Gly 190	Ala	Tyr
25	Gly	Gly	Ile 195	Phe	Val	Val	Ala	Arg 200	Arg	Ala	Ala	Leu	Arg 205	Pro	Pro	Arg
	Pro	Ala 210	Arg	Gly	Ser	Arg	Leu 215	Arg	Ser	Asp	Ser	Leu 220	Asp	Ser	Arg	Leu
30	Ser 225	Ile	Leu	Pro	Pro	Leu 230	Arg	Pro	Arg	Leu	Pro 235	Gly	Gly	Lys	Ala	Ala 240
	Leu	Ala	Pro		Leu 245	Ala	Val	Gly	Gln	Phe 250	Ala	Ala	Cys	Trp	Leu 255	Pro
	Tyr	Gly	Cys	Ala 260	Cys	Leu	Ala	Pro	Ala 265	Ala	Arg	Ala	Ala	Glu 270	Ala	Glu
35	Ala	Ala	Val 275	Thr	Trp	Val	Ala	Tyr 280	Ser	Ala	Phe	Ala	Ala 285	His	Pro	Phe
	Leu	Tyr	Gly	Leu	Leu	Gln	Arg	Pro	Val	Arg	Leu	Ala	Leu	Gly	Arg	Leu

295

-9-

300

Ser Arg Arg Ala Leu Pro Gly Pro Val Arg Ala Cys Thr Pro Gln Ala 305 310 315 320

Trp His Pro Arg Ala Leu Leu Gln Cys Leu Gln Arg Pro Pro Glu Gly 325 330 335

Pro Ala Val Gly Pro Ser Glu Ala Pro Glu Gln Thr Pro Glu Leu Ala
340 345 350

Gly Gly Arg Ser Pro Ala Tyr Gln Gly Pro Pro Glu Ser Ser Leu Ser 355 360 365

10 (8) INFORMATION FOR SEQ ID NO:7:

290

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1008 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
- 15 (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

ATGGAATCAT CTTTCTCATT TGGAGTGATC CTTGCTGTCC TGGCCTCCCT CATCATTGCT 60
ACTAACACAC TAGTGGCTGT GGCTGTGCTG CTGTTGATCC ACAAGAATGA TGGTGTCAGT 120
20 CTCTGCTTCA CCTTGAATCT GGCTGTGGCT GACACCTTGA TTGGTGTGGC CATCTCTGGC 180
CTACTCACAG ACCAGCTCTC CAGCCCTTCT CGGCCCACAC AGAAGACCCT GTGCAGCCTG 240
CGGATGGCAT TTGTCACTTC CTCCGCAGCT GCCTCTGTCC TCACGGTCAT GAGTGGATCACC 300
TTTGACAGGT ACCTTGCCAT CAAGCAGCCC TTCCGCTACT TGAAGATCAT GAGTGGGTTC 360
GTGGCCGGGG CCTGCATTGC CGGGCTGTGG TTAGTGTCTT ACCTCATTGG CTTCCCCCA 420
25 CTCGGAATCC CCATGTTCCA GCAGACTGCC TACAAAGGGC AGTGCAGCTT CTTTGCTGTA 480
TTTCACCCTC ACTTCGTGCA CATGCTCCAC TGCGTTGGCT TCTTCCCAGC CATGCTCCTC 540
AAGATGGAAC ATGCAGGAG CATGCTCAAG ATTGCCTCCA TGCACAGCCA GCAGATTCGA 600
AAGATGGAAC ATGCAGGAG CATGCTGAA GGTTATCGAT CCCCACGGAC TCCCAGCGAC 660
TTCAAAAGCTC TCCGTACTGT GTCTGTTCTC ATTGGGAGCT TTGCTCTATC CTGGACCCCC 720
30 TTCCTTATCA CTGGCATTGT GCAGGTGGCC TGCCAGGAGT GTCACCTCTA CCTAGTGCTG 780

GAACGGTACC TGTGGCTGCT CGGCGTGGGC AACTCCCTGC TCAACCCACT CATCTATGCC 840

- 10 -

TATTGGCAGA AGGAGGTGCG ACTGCAGCTC TACCACATGG CCCTAGGAGT GAAGAAGGTG 900
CTCACCTCAT TCCTCCTCTT TCTCTCGGCC AGGAATTGTG GCCCAGAGAG GCCCAGGGAA 960
AGTTCCTGTC ACATCGTCAC TATCTCCAGC TCAGAGTTTG ATGGCTAA 1008

- (9) INFORMATION FOR SEQ ID NO:8:
- 5 (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 335 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: not relevant
- 10 (ii) MOLECULE TYPE: protein
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Glu Ser Ser Phe Ser Phe Gly Val Ile Leu Ala Val Leu Ala Ser 1 5 10 15

Leu Ile Ile Ala Thr Asn Thr Leu Val Ala Val Ala Val Leu Leu Leu 15 20 25 30

Ile His Lys Asn Asp Gly Val Ser Leu Cys Phe Thr Leu Asn Leu Ala 35 40 45

Val Ala Asp Thr Leu Ile Gly Val Ala Ile Ser Gly Leu Leu Thr Asp 50 55 60

20 Gln Leu Ser Ser Pro Ser Arg Pro Thr Gln Lys Thr Leu Cys Ser Leu 65 70 75 80

Arg Met Ala Phe Val Thr Ser Ser Ala Ala Ala Ser Val Leu Thr Val 85 90 95

Met Leu Ile Thr Phe Asp Arg Tyr Leu Ala Ile Lys Gln Pro Phe Arg 25 100 105 110

Tyr Leu Lys Ile Met Ser Gly Phe Val Ala Gly Ala Cys Ile Ala Gly 115 120 125

Leu Trp Leu Val Ser Tyr Leu Ile Gly Phe Leu Pro Leu Gly Ile Pro 130 135 140

Met Phe Gln Gln Thr Ala Tyr Lys Gly Gln Cys Ser Phe Phe Ala Val

Pre His Pro His Phe Val Leu Thr Leu Ser Cys Val Gly Phe Phe Pro 165 170 175

Ala Met Leu Leu Phe Val Phe Phe Tyr Cys Asp Met Leu Lys Ile Ala 35 180 185 190

•••

- 11 -

- Ser Met His Ser Gln Gln Ile Arg Lys Met Glu His Ala Gly Ala Met 195 200 205
- Ala Gly Gly Tyr Arg Ser Pro Arg Thr Pro Ser Asp Phe Lys Ala Leu 210 215 220
- Arg Thr Val Ser Val Leu Ile Gly Ser Phe Ala Leu Ser Trp Thr Pro 225 230 235 240
 - Phe Leu Ile Thr Gly Ile Val Gln Val Ala Cys Gln Glu Cys His Leu
 245 250 255
- Tyr Leu Val Leu Glu Arg Tyr Leu Trp Leu Leu Gly Val Gly Asn Ser 10 265 270
 - Leu Leu Asn Pro Leu Ile Tyr Ala Tyr Trp Gln Lys Glu Val Arg Leu 275 280 285
 - Gln Leu Tyr His Met Ala Leu Gly Val Lys Lys Val Leu Thr Ser Phe 290 295 300
- Leu Leu Phe Leu Ser Ala Arg Asn Cys Gly Pro Glu Arg Pro Arg Glu 305 310 315 320
 - Ser Ser Cys His Ile Val Thr Ile Ser Ser Ser Glu Phe Asp Gly 325 330 330
 - (10) INFORMATION FOR SEQ ID NO:9:

- 20 (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1413 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ATGGACACTA CCATGGAAGC TGACCTGGGT GCCACTGGCC ACAGGCCCCG CACAGAGCTT 60
GATGATGAGG ACTCCTACCC CCAAGGTGGC TGGGACACGG TCTTCCTGGT GGCCCTGCTG 120
CTCCTTGGGC TGCCAGCCAA TGGGTTGATG GCGTGGCTG CCGGCTCCCA GGCCCGGCAT 180
30 GGAGCTGGCA CGCGTCTGC GCTGCTCCTG CTCAGCCTGG CCCTCTCTGA CTTCTTGTTC 240
CTGGCAGCAG CGGCCTTCCA GATCCTAGAG ATCCGGCATG GGGGACACTG GCCGCTGGGG 300
ACAGCTGCCT GCCGCTTCTA CTACTTCCTA TGGGGCGTGT CCTACTCCTC CGGCCTCTC 360
CTGCTGGCCG CCCTCAGCCT CGACCGCTGC CTGCTGGCGC TGTGCCCACA CTGGTACCCT 420
GGGCACCGCC CAGTCCGCCT GCCCCTCTGG GTCTGCGCCG GTGTCTGGGT GCTGGCCACA 480

- 12 -

CTCTTCAGCG TGCCCTGGCT GGTCTTCCCC GAGGCTGCCG TCTGGTGGTA CGACCTGGTC 540 ATCTGCCTGG ACTTCTGGGA CAGCGAGGAG CTGTCGCTGA GGATGCTGGA GGTCCTGGGG 600 GGCTTCCTGC CTTTCCTCCT GCTGCTCGTC TGCCACGTGC TCACCCAGGC CACAGCCTGT 660 CGCACCTGCC ACCGCCAACA GCAGCCCGCA GCCTGCCGGG GCTTCGCCCG TGTGGCCAGG 720 5 ACCATTCTGT CAGCCTATGT GGTCCTGAGG CTGCCCTACC AGCTGGCCCA GCTGCTCTAC 780 CTGGCCTTCC TGTGGGACGT CTACTCTGGC TACCTGCTCT GGGAGGCCCT GGTCTACTCC 840 GACTACCTGA TCCTACTCAA CAGCTGCCTC AGCCCCTTCC TCTGCCTCAT GGCCAGTGCC 900 GACCTCCGGA CCCTGCTGCG CTCCGTGCTC TCGTCCTTCG CGGCAGCTCT CTGCGAGGAG 960 CGGCCGGCA GCTTCACGCC CACTGAGCCA CAGACCCAGC TAGATTCTGA GGGTCCAACT1020 10 CTGCCAGAGC CGATGGCAGA GGCCCAGTCA CAGATGGATC CTGTGGCCCA GCCTCAGGTG1080 AACCCCACAC TCCAGCCACG ATCGGATCCC ACAGCTCAGC CACAGCTGAA CCCTACGGCC1140 CAGCCACAGT CGGATCCCAC AGCCCAGCCA CAGCTGAACC TCATGGCCCA GCCACAGTCA1200 GATTCTGTGG CCCAGCCACA GGCAGACACT AACGTCCAGA CCCCTGCACC TGCTGCCAGT1260 TCTGTGCCCA GTCCCTGTGA TGAAGCTTCC CCAACCCCAT CCTCGCATCC TACCCCAGGG1320 15 GCCCTTGAGG ACCCAGCCAC ACCTCCTGCC TCTGAAGGAG AAAGCCCCAG CAGCACCCCG1380 CCAGAGGCGG CCCCGGGCGC AGGCCCCACG TGA 1413

(11) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 468 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:

20

- (D) TOPOLOGY: not relevant
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:
- 25 Met Asp Thr Thr Met Glu Ala Asp Leu Gly Ala Thr Gly His Arg Pro 1 5 10 15
 - Arg Thr Glu Leu Asp Asp Glu Asp Ser Tyr Pro Gln Gly Gly Trp Asp 20 25 30
- Thr Val Phe Leu Val Ala Leu Leu Leu Gly Leu Pro Ala Asn Gly 30 $$ 35 $$ 40 $$ 45

Leu Met Ala Trp Leu Ala Gly Ser Gln Ala Arg His Gly Ala Gly Thr

- 13 -

		50					55					60				
	Arg 65	Leu	Ala	Leu	Leu	Leu 70	Leu	Ser	Leu	Ala	Leu 75	Ser	Asp	Phe	Leu	Phe 80
5	Leu	Ala	Ala	Ala	Ala 85	Phe	Gln	Ile	Leu	Glu 90	Ile	Arg	His	Gly	Gly 95	Hie
	Trp	Pro	Leu	Gly 100	Thr	Ala	Ala	Суз	Arg 105		Tyr	Tyr	Phe	Leu 110		Gly
	Val	Ser	Tyr 115	Ser	Ser	Gly	Leu	Phe 120		Leu	Ala	Ala	Leu 125		Leu	Asp
10	Arg	Cys 130	Leu	Leu	Ala	Leu	Cys 135	Pro	His	Trp	Tyr	Pro 140		His	Arg	Pro
	Val 145	Arg	Leu	Pro	Leu	Trp 150		Cys	Ala	Gly	Val 155		Val	Leu	Ala	Thr 160
15	Leu	Phe	Ser	Val	Pro 165	Trp	Leu	Val	Phe	Pro 170	Glu	Ala	Ala	Val	Trp 175	
	Tyr	Asp	Leu	Val 180	Ile	Cys	Leu	Asp	Phe 185		Asp	Ser	Glu	Glu 190	Leu	Ser
	Leu	Arg	Met 195	Leu	Glu	Val	Leu	Gly 200	Gly	Phe	Leu	Pro	Phe 205	Leu	Leu	Leu
20	Leu	Val 210	Сув	His	Val	Leu	Thr 215	Gln	Ala	Thr	Arg	Thr 220	Cys	His	Arg	Gln
	Gln 225	Gln	Pro	Ala	Ala	Cys 230	Arg	Gly	Phe	Ala	Arg 235	Val	Ala	Arg	Thr	Ile 240
25	Leu	Ser	Ala	Tyr	Val 245	Val	Leu	Arg	Leu	Pro 250	Tyr	Gln	Leu	Ala	Gln 255	Leu
	Leu	Tyr	Leu	Ala 260	Phe	Leu	Trp	Asp	Val 265	Tyr	Ser	Gly	Tyr	Leu 270	Leu	Trp
	Glu	Ala	Leu 275	Val	Tyr	Ser	Asp	Tyr 280	Leu	Ile	Leu	Leu	Asn 285	Ser	Сув	Leu
30	Ser	Pro 290	Phe	Leu	Cys	Leu	Met 295	Ala	Ser	Ala	Asp	Leu 300	Arg	Thr	Leu	Leu
	Arg 305	Ser	Val	Leu	Ser	Ser 310	Phe	Ala	Ala	Ala	Leu 315	Cys	Glu	Glu	Arg	Pro 320
35	Gly	Ser	Phe	Thr	Pro 325	Thr	Glu	Pro	Gln	Thr 330	Gln	Leu	Asp	Ser	Glu 335	Gly
	Pro	Thr	Leu	Pro 340	Glu	Pro	Met	Ala	Glu 345	Ala	Gln	Ser	Gln	Met 350	Asp	Pro

. . . 5

- 14 -

Val Ala Gln Pro Gln Val Asn Pro Thr Leu Gln Pro Arg Ser Asp Pro 355 360 365

- Thr Ala Gln Pro Gln Leu Asn Pro Thr Ala Gln Pro Gln Ser Asp Pro 370 375 380
- 5 Thr Ala Gln Pro Gln Leu Asn Leu Met Ala Gln Pro Gln Ser Asp Ser 385 390 395 400
 - Val Ala Gln Pro Gln Ala Asp Thr Asn Val Gln Thr Pro Ala Pro Ala 405 410 415
- Ala Ser Ser Val Pro Ser Pro Cys Asp Glu Ala Ser Pro Thr Pro Ser 10 420 425 430
 - Ser His Pro Thr Pro Gly Ala Leu Glu Asp Pro Ala Thr Pro Pro Ala 435 440 445
 - Ser Glu Gly Glu Ser Pro Ser Ser Thr Pro Pro Glu Ala Ala Pro Gly
 450 455 460
- 15 Ala Gly Pro Thr
 - (12) INFORMATION FOR SEQ ID NO:11:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1248 base pairs
- 20 (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:
- 25 ATGTCAGGGA TGGAAAAACT TCAGAATGCT TCCTGGATCT ACCAGCAGAA ACTAGAAGAT 60

 CCATTCCAGA AACACCTGAA CAGCACCGAG GAGTATCTGG CCTTCCTCTG CGGACCTCGG 120

 CGCAGCCACT TCTTCCTCCC CGTGTCTGTG GTGTATGTGC CAATTTTTGT GGTGGGGGTC 180

 ATTGGCAATG TCCTGGTGTG CCTGGTGATT CTGCAGCACC AGGCTATGAA GACGCCCACC 240

 AACTACTACC TCTTCAGCCT GGCGGTCTCT GACCTCCTGG TCCTGCTCCT TGGAATGCCC 300

 30 CTGGAAGGTCT ATGAGATGTG GCGCAACTAC CCTTTCTTGT TCGGGCCCGT GGGCTGCTAC 360

 TTCAAGACGG CCCTCTTTGA GACCGTGTGC TTCGCCTCCA TCCTCAGCAT CACCACCGTC 420

 AGCGTGGAGC GCTACGTGGC CATCCTACAC CCGTTCCGCG CCAAACTGCA GAGCACCCGG 480

 CGCCGGGCCC TCAGGATCCT CGGCATCGTC TGGGGCTTCT CTCCCTGCCC 540

- 15 -

AACACCAGCA TCCATGGCAT CAAGTTCCAC TACTTCCCCA ATGGGTCCCT GGTCCCAGGT 600
TCGGCCACCT GTACGGTCAT CAAGCCCATG TGGATCTACA ATTTCATCAT CCCAGGTCACC 660
TCCTTCCTAT TCTACCTCCT CCCCATGACT GTCATCAGTG TCCTCTACTA CCTCATGGCA 720
CTCAGACTAA AGAAAGACAA ATCTCTTGAG GCAGATGAAG GGAATGCAAA TATTCAAAGA 780
CCCTGCAGAA AATCAGTCAA CAAGATGCTG TTTGTCTTGG TCTTAGTGTT TGCTATCTGT 840
TGGGCCCCGT TCCACATTGA CCGACTCTTC TTCAGCTTTG TGGAGGAGTG GAGTGAATCC 900
CTGGCTGCTG TGTTCAACCT CGTCCATGTG GTGTCAGGTG TCTTCTTCTA CCTGAGCTCA 960
GCTGTCAACC CCATTATCTA TAACCTACTG TCTCGCCGCT TCCAGGCAGC ATTCCAGAAT1.020
GTGATCTCTT CTTTCCACAA ACAGTGGCAC TCCCAGCATG ACCCACAGTT GCCACCTGCC1.080
10 CAGCGGAACA TCTTCCTGAC AGAATGCCAC TTTGTGGAGC TGACCGAAGA TATAGGTCCC1.140
CAATTCCCAT GTCAGTCATC CATGCACAAC TCTCACCTCC CAACAGCCCT CTCTAGTGAA12.00
CAGATGTCAA GAACAAACTA TCAAAGCTTC CACTTTAACA AAACCTGA TAACCTGAA1.200

(13) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

15

- (A) LENGTH: 415 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: not relevant
- (ii) MOLECULE TYPE: protein
- 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Ser Gly Met Glu Lys Leu Gln Asn Ala Ser Trp Ile Tyr Gln Gln 1 5 15

Lys Leu Glu Asp Pro Phe Gln Lys His Leu Asn Ser Thr Glu Glu Tyr 20 25 30

25 Leu Ala Phe Leu Cys Gly Pro Arg Arg Ser His Phe Phe Leu Pro Val 35 40 45

Ser Val Val Tyr Val Pro Ile Phe Val Val Gly Val Ile Gly Asn Val 50 55 60

Leu Val Cys Leu Val Ile Leu Gln His Gln Ala Met Lys Thr Pro Thr 30 65 70 75 80

Asn Tyr Tyr Leu Phe Ser Leu Ala Val Ser Asp Leu Leu Val Leu Leu 85 90 95

	Leu	Gly	Met	Pro 100		Glu	Val	Tyr	Glu 105		Trp	Arg	Asn	Tyr 110		Phe
	Leu	Phe	Gly 115	Pro	Val	Gly	Cys	Туг 120	Phe	Lys	Thr	Ala	Leu 125		Glu	Thr
5	Val	Cys 130	Phe	Ala	Ser	Ile	Leu 135		Ile	Thr	Thr	Val 140		Val	Glu	Arg
	Tyr 145	Val	Ala	Ile	Leu	His 150	Pro	Phe	Arg	Ala	Lys 155	Leu	Gln	Ser	Thr	Arg 160
10	Arg	Arg	Ala	Leu	Arg 165	Ile	Leu	Gly	Ile	Val 170	Trp	Gly	Phe	Ser	Val 175	Leu
	Phe	Ser	Leu	Pro 180	Asn	Thr	Ser	Ile	His 185	Gly	Ile	Lys	Phe	His 190		Phe
	Pro	Asn	Gly 195	Ser	Leu	Val	Pro	Gly 200	Ser	Ala	Thr	СЛа	Thr 205	Val	Ile	Lys
15	Pro	Met 210	Trp	Ile	Tyr	Asn	Phe 215	Ile	Ile	Gln	Val	Thr 220	Ser	Phe	Leu	Phe
	Tyr 225	Leu	Leu	Pro	Met	Thr 230	Val	Ile	Ser	Val	Leu 235	Tyr	Tyr	Leu	Met	Ala 240
20	Leu	Arg	Leu	Lys	Lys 245	Asp	Lys	Ser	Leu	Glu 250	Ala	Asp	Glu	Gly	Asn 255	Ala
	Asn	Ile	Gln	Arg 260	Pro	Сув	Arg	Lys	Ser 265	Val	Asn	Lys	Met	Leu 270	Phe	Val
	Leu	Val	Leu 275	Val	Phe	Ala	Ile	Cys 280	Trp	Ala	Pro	Phe	His 285	Ile	Asp	Arg
25	Leu	Phe 290	Phe	Ser	Phe	Val	Glu 295	Glu	Ттр	Ser	Glu	Ser 300	Leu	Ala	Ala	Val
	Phe 305	Asn.	Leu	Val	His	Val 310	Val	Ser	Gly	Val	Phe 315	Phe	Tyr	Leu	Ser	Ser 320
30	Ala	Val	Asn	Pro	Ile 325	Ile	Tyr	Asn	Leu	Leu 330	Ser	Arg	Arg	Phe	Gln 335	Ala
	Ala	Phe	Gln	Asn 340	Val	Ile	Ser	Ser	Phe	His	Lys	Gln	Trp	His 350	Ser	Gln
	His	Asp	Pro 355		Leu	Pro	Pro	Ala 360		Arg	Asn	Ile	Phe 365		Thr	Glu
35	Суз	His 370	Phe	Val	Glu	Leu	Thr 375	Glu	qaA	Ile	Gly	Pro 380	Gln	Phe	Pro	Сув
	Gln 385	Ser	Ser	Met		Asn 390	Ser	His	Leu	Pro	Thr 395	Ala	Leu	Ser	Ser	Glu 400

- `

- 17 -

Gln Met Ser Arg Thr Asn Tyr Gln Ser Phe His Phe Asn Lys Thr 405 410 415

(14) INFORMATION FOR SEQ ID NO:13:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1173 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

ATGCCAGATA CTAATAGCAC AATCAATTTA TCACTAAGCA CTCGTGTTAC TTTAGCATTT 60 TTTATGTCCT TAGTAGCTTT TGCTATAATG CTAGGAAATG CTTTGGTCAT TTTAGCTTTT 120 GTGGTGGACA AAAACCTTAG ACATCGAAGT AGTTATTTTT TTCTTAACTT GGCCATCTCT 180 GACTTCTTTG TGGGTGTGAT CTCCATTCCT TTGTACATCC CTCACACGCT GTTCGAATGG 240 15 GATTTTGGAA AGGAAATCTG TGTATTTTGG CTCACTACTG ACTATCTGTT ATGTACAGCA 300 TCTGTATATA ACATTGTCCT CATCAGCTAT GATCGATACC TGTCAGTCTC AAATGCTGTG 360 TCTTATAGAA CTCAACATAC TGGGGTCTTG AAGATTGTTA CTCTGATGGT GGCCGTTTGG 420 GTGCTGGCCT TCTTAGTGAA TGGGCCAATG ATTCTAGTTT CAGAGTCTTG GAAGGATGAA 480 GGTAGTGAAT GTGAACCTGG ATTTTTTTCG GAATGGTACA TCCTTGCCAT CACATCATTC 540 20 TTGGAATTCG TGATCCCAGT CATCTTAGTC GCTTATTTCA ACATGAATAT TTATTGGAGC 600 CTGTGGAAGC GTGATCATCT CAGTAGGTGC CAAAGCCATC CTGGACTGAC TGCTGTCTCT 660 TCCAACATCT GTGGACACTC ATTCAGAGGT AGACTATCTT CAAGGAGATC TCTTTCTGCA 720 TCGACAGAAG TTCCTGCATC CTTTCATTCA GAGAGACAGA GGAGAAAGAG TAGTCTCATG 780 TTTTCCTCAA GAACCAAGAT GAATAGCAAT ACAATTGCTT CCAAAATGGG TTCCTTCTCC 840 25 CAATCAGATT CTGTAGCTCT TCACCAAAGG GAACATGTTG AACTGCTTAG AGCCAGGAGA 900 TTAGCCAAGT CACTGGCCAT TCTCTTAGGG GTTTTTGCTG TTTGCTGGGC TCCATATTCT 960 CTGTTCACAA TTGTCCTTTC ATTTTATTCC TCAGCAACAG GTCCTAAATC AGTTTGGTAT1020 AGAATTGCAT TTTGGCTTCA GTGGTTCAAT TCCTTTGTCA ATCCTCTTTT GTATCCATTG1080 TGTCACAAGC GCTTTCAAAA GGCTTTCTTG AAAATATTTT GTATAAAAAA GCAACCTCTA1140 30 CCATCACAAC ACAGTCGGTC AGTATCTTCT TAA 1173

• •

(15) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 390 amino acids
 - (B) TYPE: amino acid
- (C) STRANDEDNESS:

- (D) TOPOLOGY: not relevant
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:
- Met Pro Asp Thr Asn Ser Thr Ile Asn Leu Ser Leu Ser Thr Arg Val $10 \hspace{1.5cm} 1 \hspace{1.5cm} 5 \hspace{1.5cm} 10 \hspace{1.5cm} 15 \hspace{1.5cm} 15$
 - Thr Leu Ala Phe Phe Met Ser Leu Val Ala Phe Ala Ile Met Leu Gly 20 25 30
 - Asn Ala Leu Val Ile Leu Ala Phe Val Val Asp Lys Asn Leu Arg His $35 \hspace{1cm} 40 \hspace{1cm} 45$
- 15 Arg Ser Ser Tyr Phe Phe Leu Asn Leu Ala Ile Ser Asp Phe Phe Val
 - Gly Val Ile Ser Ile Pro Leu Tyr Ile Pro His Thr Leu Phe Glu Trp 65 70 75 80
- Asp Phe Gly Lys Glu Ile Cys Val Phe Trp Leu Thr Thr Asp Tyr Leu 20 $$ 85 $$ 90 $$ 95
 - Leu Cys Thr Ala Ser Val Tyr Asn Ile Val Leu Ile Ser Tyr Asp Arg
 - Tyr Leu Ser Val Ser Asn Ala Val Ser Tyr Arg Thr Gln His Thr Gly
 115 120 125
- Val Leu Lys Ile Val Thr Leu Met Val Ala Val Trp Val Leu Ala Phe 130 135 140
 - Leu Val Asn Gly Pro Met Ile Leu Val Ser Glu Ser Trp Lys Asp Glu 145 150 155 160
- Gly Ser Glu Cys Glu Pro Gly Phe Phe Ser Glu Trp Tyr Ile Leu Ala 30 $$ 165 $$ 170 $$ 175
 - Ile Thr Ser Phe Leu Glu Phe Val Ile Pro Val Ile Leu Val Ala Tyr 180 185 190
 - Phe Asn Met Asn Ile Tyr Trp Ser Leu Trp Lys Arg Asp His Leu Ser 195 200 205
- Arg Cys Gln Ser His Pro Gly Leu Thr Ala Val Ser Ser Asn Ile Cys 210 215 220

. • •

- 19 -

Gly His Ser Phe Arg Gly Arg Leu Ser Ser Arg Arg Ser Leu Ser Ala 230 235 Ser Thr Glu Val Pro Ala Ser Phe His Ser Glu Arg Gln Arg Arg Lys 250 Ser Ser Leu Met Phe Ser Ser Arg Thr Lys Met Asn Ser Asn Thr Ile 265 Ala Ser Lys Met Gly Ser Phe Ser Gln Ser Asp Ser Val Ala Leu His Gln Arg Glu His Val Glu Leu Leu Arg Ala Arg Arg Leu Ala Lys Ser 10 295 Leu Ala Ile Leu Leu Gly Val Phe Ala Val Cys Trp Ala Pro Tyr Ser Leu Phe Thr Ile Val Leu Ser Phe Tyr Ser Ser Ala Thr Gly Pro Lys 15 Ser Val Trp Tyr Arg Ile Ala Phe Trp Leu Gln Trp Phe Asn Ser Phe Val Asn Pro Leu Leu Tyr Pro Leu Cys His Lys Arg Phe Gln Lys Ala Phe Leu Lys Ile Phe Cys Ile Lys Lys Gln Pro Leu Pro Ser Gln His 20 375 Ser Arg Ser Val Ser Ser

(16) INFORMATION FOR SEQ ID NO:15:

25

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1128 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
- 30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

ATGGGGAACG CGAGCGAGCC GGGTGGCAGC GGCGGCGGC AGGCGGCCGC CCTGGGCCTC 60

AAGCTGGCCA CGCTCAGCCT GCTGCTGTGC GTGAGCCTAG CGGGCAACGT GCTGTTCGCG 120

CTGCTGATCG TGCGGGAGCG CAGCCTGCAC CGCGCCCCGT ACTACCTGCT GCTCGACCTG 180

TGCCTGGCCG ACGGCTGCG CGCGCTCGCC TGCCTCCCGG CCGTCATGCT GGCGGCGCGG 240

35 CGTGCGGCGG CCGCGCGGG GGCGCCGCG GGCGCGCTGG GCTGCAAGCT GCTCGCCTTC 300

TACCTGGCGGC TCTTCTGCTT CCACGCCGC TTCCTGCTGC TGGGCGTGG CGTCACCCGC 360

TACCTGGCCA TCGCGCACCA CCGCTTCTAT GCAGAGCGCC TGGCCGGCTG GCCGTGCGCC 420

GCCATGCTGG TGTGCGCCGC CTGGGCGCTG GCGCTGGCCG CGGCCTTCCC GCCAGTGCTG 480

GACGGCGGTG GCGACGACGA GGACGCGCG TGCGCCCTGG AGCAGCGGCC CGACGGCGCC 540

5 CCCGGCGGCGC TGGGCTTCCT GCTGCTGCTG GCCGTGGTG TGGGCCGCC GCACCTCGTC 600

TACCTCCGCC TGCTCTTCTT CATCCACGAC CGCCGCAAGA TGCGGCCCG GCGCCTGGTG 660

CCCGCCGTCA GCCACGACTG GACCTTCCAC GGCCCGGGCG CCACCGGCCA GGCGCCGCC 720

AACTGGACGG CGGGCTTCGG CCGCGGGCCC ACGCCGCCG CGCTTGTGGG CATCCGGCC 780

GCAGGGCCGG GCCGCGGCG CCGCCGCCC CTCGTGTGG AAGAATTCAA GACGGAGAAG 840

10 AGGCTGTGCA AGATGTTCTA CGCCGTCACG CTGCTCTCC TGCTCCTCTG GGGGCCCTAC 900

GTCGTGGCCA GCTACCTGCG GGTCCTGGTG CGGCCCGGCG CCGTCCCCCA GGCCTACCTG 960

ACGGCCTCCG TGTGGCTGAC CTTCGCGCAG GCCCGGCTCC CCGTCCCCA GGCCTTCCTC1020

TTCAACAGGG AGCTGAGGA CTGCTTCAGG GCCCAGTTCC CCTGCTGCCA GAGCCCCCGG1080

ACCACCCAGG CGGCCCCCC CTGCGACCTG CCCCAGTTCC CCTGCTGCCA GAGCCCCCGG1080

ACCACCCAGG CGGCCCCCC CTGCGACCTG AAAGGCATTG CCTGCTGCCA GAGCCCCCGG1080

15 (17) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 375 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
- 20 (D) TOPOLOGY: not relevant
 - (ii) MOLECULE TYPE: protein

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Ala Asn Ala Ser Glu Pro Gly Gly Ser Gly Gly Glu Ala Ala 1 5 10 15

25 Ala Leu Gly Leu Lys Leu Ala Thr Leu Ser Leu Leu Leu Cys Val Ser
20 25 30

Leu Ala Gly Asn Val Leu Phe Ala Leu Leu Ile Val Arg Glu Arg Ser 35 40 45

Leu His Arg Ala Pro Tyr Tyr Leu Leu Leu Asp Leu Cys Leu Ala Asp 50 55 60

Gly Leu Arg Ala Leu Ala Cys Leu Pro Ala Val Met Leu Ala Ala Arg 65 70 75 80

	Arg	Ala	Ala	Ala	Ala 85	Ala	Gly	Ala	Pro	Pro 90	Gly	Ala	Leu	Gly	Сув 95	Lys
	Leu	Leu	Ala	Phe 100	Leu	Ala	Ala	Leu	Phe 105	Cys	Phe	His	Ala	Ala 110	Phe	Leu
5	Leu	Leu	Gly 115	Val	Gly	Val	Thr	Arg 120	туг	Leu	Ala	Ile	Ala 125	His	His	Arg
	Phe	Tyr 130	Ala	Glu	Arg	Leu	Ala 135	Gly	Trp	Pro	Cys	Ala 140	Ala	Met	Leu	Val
10	Cys 145	Ala	Ala	Trp	Ala	Leu 150	Ala	Leu	Ala	Ala	Ala 155	Phe	Pro	Pro	Val	Leu 160
	Asp	Gly	Gly	Gly	Asp 165	Asp	Glu	Asp	Ala	Pro 170	Cys	Ala	Leu	Glu	Gln 175	Arg
	Pro	Asp	Gly	Ala 180	Pro	Gly	Ala	Leu	Gly 185	Phe	Leu	Leu	Leu	Leu 190	Ala	Val
15	Val	Val	Gly 195	Ala	Thr	His	Leu	Val 200	Tyr	Leu	Arg	Leu	Leu 205	Phe	Phe	Ile
	His	Asp 210	Arg	Arg	Lys	Met	Arg 215	Pro	Ala	Arg	Leu	Val 220	Pro	Ala	Val	Ser
20	His 225	Asp	Trp	Thr	Phe	His 230	Gly	Pro	Gly	Ala	Thr 235	Gly	Gln	Ala	Ala	Ala 240
	Asn	Trp	Thr	Ala	Gly 245	Phe	Gly	Arg	Gly	Pro 250	Thr	Pro	Pro	Ala	Leu 255	Val
	Gly	Ile	Arg	Pro 260	Ala	Gly	Pro	Gly	Arg 265	Gly	Ala	Arg	Arg	Leu 270	Leu	Val
25	Leu	Glu	Glu 275	Phe	Lys	Thr	Glu	Lys 280	Arg	Leu	Cys	Lys	Met 285	Phe	Tyr	Ala
	Val	Thr. 290	Leu	Leu	Phe	Leu	Leu 295	Leu	Trp	Gly	Pro	Tyr 300	Val	Val	Ala	Ser
30	Tyr 305	Leu	Arg	Val	Leu	Val 310	Arg	Pro	Gly	Ala	Val 315	Pro	Gln	Ala	Tyr	Leu 320
	Thr	Ala	Ser	Val	Trp 325	Leu	Thr	Phe	Ala	Gln 330	Ala	Gly	Ile	Asn	Pro 335	Val
	Val	Сув	Phe	Leu 340	Phe	Asn	Arg	Glu	Leu 345	Arg	Asp	Сув	Phe	Arg 350	Ala	Gln
35	Phe	Pro	Cys 355	Cys	Gln	Ser	Pro	Arg 360	Thr	Thr	Gln	Ala	Thr 365	His	Pro	Cys
	Asp	Leu	Lys	Gly	Ile	Gly	Leu									

5

30

370

- (18) INFORMATION FOR SEQ ID NO:17:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1002 base pairs
- (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:
- 10 ATGAACACCA CAGTGATGCA AGGCTTCAAC AGATCTGAGC GGTGCCCCAG AGACACTCGG 60 ATAGTACAGC TGGTATTCCC AGCCCTCTAC ACAGTGGTTT TCTTGACCGG CATCCTGCTG 120 AATACTTTGG CTCTGTGGGT GTTTGTTCAC ATCCCCAGCT CCTCCACCTT CATCATCTAC 180 CTCAAAAACA CTTTGGTGGC CGACTTGATA ATGACACTCA TGCTTCCTTT CAAAATCCTC 240 TCTGACTCAC ACCTGGCACC CTGGCAGCTC AGAGCTTTTG TGTGTCGTTT TTCTTCGGTG 300 15 ATATTTTATG AGACCATGTA TGTGGGCATC GTGCTGTTAG GGCTCATAGC CTTTGACAGA 360 TTCCTCAAGA TCATCAGACC TTTGAGAAAT ATTTTTCTAA AAAAACCTGT TTTTGCAAAA 420 ACGGTCTCAA TCTTCATCTG GTTCTTTTTG TTCTTCATCT CCCTGCCAAA TACGATCTTG 480 AGCAACAAGG AAGCAACACC ATCGTCTGTG AAAAAGTGTG CTTCCTTAAA GGGGCCTCTG 540 GGGCTGAAAT GGCATCAAAT GGTAAATAAC ATATGCCAGT TTATTTTCTG GACTGTTTTT 600 20 ATCCTAATGC TTGTGTTTTA TGTGGTTATT GCAAAAAAG TATATGATTC TTATAGAAAG 660 TCCAAAAGTA AGGACAGAAA AAACAACAAA AAGCTGGAAG GCAAAGTATT TGTTGTCGTG 720 GCTGTCTTCT TTGTGTGTTT TGCTCCATTT CATTTTGCCA GAGTTCCATA TACTCACAGT 780 CAAACCAACA ATAAGACTGA CTGTAGACTG CAAAATCAAC TGTTTATTGC TAAAGAAACA 840 ACTCTCTTTT TGGCAGCAAC TAACATTTGT ATGGATCCCT TAATATACAT ATTCTTATGT 900 25 AAAAAATTCA CAGAAAAGCT ACCATGTATG CAAGGGAGAA AGACCACAGC ATCAAGCCAA 960 GAAAATCATA GCAGTCAGAC AGACAACATA ACCTTAGGCT GA 1002
 - (19) INFORMATION FOR SEQ ID NO:18:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 333 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:

- 23 -

(D) TOPOLOGY: not relevant (ii) MOLECULE TYPE: protein (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18: Met Asn Thr Thr Val Met Gln Gly Phe Asn Arg Ser Glu Arg Cys Pro 5 10 Arg Asp Thr Arg Ile Val Gln Leu Val Phe Pro Ala Leu Tyr Thr Val 25 Val Phe Leu Thr Gly Ile Leu Leu Asn Thr Leu Ala Leu Trp Val Phe 10 Val His Ile Pro Ser Ser Ser Thr Phe Ile Ile Tyr Leu Lys Asn Thr 55 Leu Val Ala Asp Leu Ile Met Thr Leu Met Leu Pro Phe Lys Ile Leu 70 Ser Asp Ser His Leu Ala Pro Trp Gln Leu Arg Ala Phe Val Cys Arg 15 Phe Ser Ser Val Ile Phe Tyr Glu Thr Met Tyr Val Gly Ile Val Leu 105 Leu Gly Leu Ile Ala Phe Asp Arg Phe Leu Lys Ile Ile Arg Pro Leu 20 Arg Asn Ile Phe Leu Lys Lys Pro Val Phe Ala Lys Thr Val Ser Ile Phe Ile Trp Phe Phe Leu Phe Phe Ile Ser Leu Pro Asn Thr Ile Leu Ser Asn Lys Glu Ala Thr Pro Ser Ser Val Lys Lys Cys Ala Ser Leu 25 Lys Gly Pro Leu Gly Leu Lys Trp His Gln Met Val Asn Asn Ile Cys 185 Gln Phe Ile Phe Trp Thr Val Phe Ile Leu Met Leu Val Phe Tyr Val 200 30 Val Ile Ala Lys Lys Val Tyr Asp Ser Tyr Arg Lys Ser Lys Asp Arg Lys Asn Asn Lys Lys Leu Glu Gly Lys Val Phe Val Val Val 230

- 0

. 245

35

Ala Val Phe Phe Val Cys Phe Ala Pro Phe His Phe Ala Arg Val Pro

- 24 -

Tyr Thr His Ser Gln Thr Asn Asn Lys Thr Asp Cys Arg Leu Gln Asn 260 265 270

Gln Leu Phe Ile Ala Lys Glu Thr Thr Leu Phe Leu Ala Ala Thr Asn 275 280 285

5 Ile Cys Met Asp Pro Leu Ile Tyr Ile Phe Leu Cys Lys Lys Phe Thr 290 295 300

Glu Lys Leu Pro Cys Met Gln Gly Arg Lys Thr Thr Ala Ser Ser Gln 305 310 315 320

Glu Asn His Ser Ser Gln Thr Asp Asn Ile Thr Leu Gly 10 325 330

(20) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1122 base pairs
 - (B) TYPE: nucleic acid
- 15 (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

20 TCAGCTTATG TGAAGCTGGT ACTGCTGGGA CTGATTATGT GCGTGAGCCT GGCGGGTAAC 120
GCCATCTTGT CCCTGCTGGT GCTCAAGGAG CTGATTATGT GCGTGAGCCT GGCGGGTAAC 120
GCCATCTTGT CCCTGCTGGT GCTCAAGGAG CGTGCCCTGC ACAAGGCTCC TTACTACTTC 180
CTGCTGGACC TGTGCCTGGC CGATGGCATA CGCTCTGCCG TCTGCTTCCC CTTTGTGCTG 240
GCTTCTGTGC GCCACGGCTC TTCATGGACC TCAGGTGCAC GATTGTGGCC 360
TTTATGGCCG TGCTCTTTTG CTTCCATGCG GCCTTCATGC TGTTCTGCAT CAGCGTCACC 360

25 CGCTACATGG CCATCGCCCA CCACCGCTTC TACGCCAAGC GCATGACACT CTGGACATGC 420
GCGGCTGTCA TCTGCATGGC CTGGACCCTG TCTGTGGCCA TGGCCTTCCC ACCTGTCTTT 480
GACGTGGGCA CCTACAAGGT TATTCGGGAG GAGGACCAGT GCATCTTTGA GCATCGCTAC 540
TTCAAGGCCA ATGACACGCT GGCCTTCATG CTTTTTGG CTGTGCTCAT GGCAGCTACC 600
CATGCTGTCT ACGGCAAGCT GCTCCTTCC GAGTATCGTC ACCGCAAGAT GAAGCCAGTG 660
30 CAGATGGTGC CAGCCATCAG CCAGAACTGG ACATTCCATG GTCCCGGGGC CACCGGCCAG 720
GCTGCTGCCA ACTGGATCGC CGGCTTTTGGC CGTGGGCCCA TGCCACCAAC CCTGCTGGT 780
ATCCCGGCAGA ATGGGCATGC CGGCTTTGGC CGGCCCAG CGCTCACGGCCAG 720
ATCCCGGCAGA ATGGGCATGC CGGCCTGC CGGCCCAG CGCTCACGGCCAG CCTGCTGGGT 780

.

- 25 -

GAAAAGCAGC TGGGCCGCAT GTTCTACGCG ATCACACTGC TCTTTCTGCT CCTCTGGTCA 900

CCCTACATCG TGGCCTGCTA CTGGCGAGTG TTTGTGAAAG CCTGTGCTGT GCCCCACCGC 960

TACCTGGCCA CTGCTGTTTG GATGAGCTTC GCCCAGGCTG CCGTCAACCC AATTGTCTGC1020

TTCCTGCTCA ACAAGGACCT CAAGAAGTGC CTGACCACTC ACGCCCCCTG CTGGGGCACA1080

5 GGAGGTGCCC CGGCTCCCAG AGAACCCTAC TGTGTCATGT GA 1122

- (21) INFORMATION FOR SEQ ID NO:20:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 373 amino acids
 - (B) TYPE: amino acid
- 10
- (C) STRANDEDNESS:
- (D) TOPOLOGY: not relevant
- (ii) MOLECULE TYPE: DNA (genomic)
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:
- Met Ala Asn Thr Thr Gly Glu Pro Glu Glu Val Ser Gly Ala Leu Ser 15 10 15
 - Pro Pro Ser Ala Ser Ala Tyr Val Lys Leu Val Leu Leu Gly Leu Ile 20 25 30
 - Met Cys Val Ser Leu Ala Gly Asn Ala Ile Leu Ser Leu Leu Val Leu 35 40 45
- 20 Lys Glu Arg Ala Leu His Lys Ala Pro Tyr Tyr Phe Leu Leu Asp Leu 50 55 60
 - Cys Leu Ala Asp Gly Ile Arg Ser Ala Val Cys Phe Pro Phe Val Leu 65 70 75 80
- Ala Ser Val Arg His Gly Ser Ser Trp Thr Phe Ser Ala Leu Ser Cys

 25 90 95
 - Lys Ile Val Ala Phe Met Ala Val Leu Phe Cys Phe His Ala Ala Phe 100 105 110
 - Met Leu Phe Cys Ile Ser Val Thr Arg Tyr Met Ala Ile Ala His His 115 120 125
- 30 Arg Phe Tyr Ala Lys Arg Met Thr Leu Trp Thr Cys Ala Ala Val Ile 130 135 140
 - Cys Met Ala Trp Thr Leu Ser Val Ala Met Ala Phe Pro Pro Val Phe 145 150 155 160
- Asp Val Gly Thr Tyr Lys Phe Ile Arg Glu Glu Asp Gln Cys Ile Phe 35 170 175

- 26 -

Glu His Arg Tyr Phe Lys Ala Asn Asp Thr Leu Gly Phe Met Leu Met 180 Leu Ala Val Leu Met Ala Ala Thr His Ala Val Tyr Gly Lys Leu Leu 200 Leu Phe Glu Tyr Arg His Arg Lys Met Lys Pro Val Gln Met Val Pro Ala Ile Ser Gln Asn Trp Thr Phe His Gly Pro Gly Ala Thr Gly Gln Ala Ala Asn Trp Ile Ala Gly Phe Gly Arg Gly Pro Met Pro Pro 10 250 Thr Leu Leu Gly Ile Arg Gln Asn Gly His Ala Ala Ser Arg Arg Leu 265 Leu Gly Met Asp Glu Val Lys Gly Glu Lys Gln Leu Gly Arg Met Phe 15 Tyr Ala Ile Thr Leu Leu Phe Leu Leu Leu Trp Ser Pro Tyr Ile Val 295 Ala Cys Tyr Trp Arg Val Phe Val Lys Ala Cys Ala Val Pro His Arg 310 Tyr Leu Ala Thr Ala Val Trp Met Ser Phe Ala Gln Ala Ala Val Asn 20 Pro Ile Val Cys Phe Leu Leu Asn Lys Asp Leu Lys Lys Cys Leu Thr 345 Thr His Ala Pro Cys Trp Gly Thr Gly Gly Ala Pro Ala Pro Arg Glu 25 Pro Tyr Cys Val Met

370

- (22) INFORMATION FOR SEQ ID NO:21:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1053 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:
- 35 ATGGCTTTGG AACAGAACCA GTCAACAGAT TATTATTATG AGGAAAATGA AATGAATGGC 60
 ACTTATGACT ACAGTCAATA TGAATTGATC TGTATCAAAG AAGATGTCAG AGAATTTGCA 120

- 27 -

AAAGTTTTCC TCCCTGTATT CCTCACAATA GCTTTCGTCA TTGGACTTGC AGGCAATTCC 180 ATGGTAGTGG CAATTTATGC CTATTACAAG AAACAGAGAA CCAAAACAGA TGTGTACATC 240 CTGAATTTGG CTGTAGCAGA TTTACTCCTT CTATTCACTC TGCCTTTTTG GGCTGTTAAT 300 GCAGTTCATG GGTGGGTTTT AGGGAAAATA ATGTGCAAAA TAACTTCAGC CTTGTACACA 360 5 CTAAACTTTG TCTCTGGAAT GCAGTTTCTG GCTTGCATCA GCATAGACAG ATATGTGGCA 420 GTAACTAATG TCCCCAGCCA ATCAGGAGTG GGAAAACCAT GCTGGATCAT CTGTTTCTGT 480 GTCTGGATGG CTGCCATCTT GCTGAGCATA CCCCAGCTGG TTTTTTATAC AGTAAATGAC 540 AATGCTAGGT GCATTCCCAT TTTCCCCCGC TACCTAGGAA CATCAATGAA AGCATTGATT 600 CAAATGCTAG AGATCTGCAT TGGATTTGTA GTACCCTTTC TTATTATGGG GGTGTGCTAC 660 10 TTTATCACGG CAAGGACACT CATGAAGATG CCAAACATTA AAATATCTCG ACCCTAAAA 720 GTTCTGCTCA CAGTCGTTAT AGTTTTCATT GTCACTCAAC TGCCTTATAA CATTGTCAAG 780 TTCTGCCGAG CCATAGACAT CATCTACTCC CTGATCACCA GCTGCAACAT GAGCAAACGC 840 ATGGACATCG CCATCCAAGT CACAGAAAGC ATTGCACTCT TTCACAGCTG CCTCAACCCA 900 ATCCTTTATG TTTTTATGGG AGCATCTTTC AAAAACTACG TTATGAAAGT GGCCAAGAAA 960 15 TATGGGTCCT GGAGAAGACA GAGACAAAGT GTGGAGGAGT TTCCTTTTGA TTCTGAGGGT1020 CCTACAGAGC CAACCAGTAC TTTTAGCATT TAA 1053

- (23) INFORMATION FOR SEQ ID NO:22:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 350 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:

20

- (D) TOPOLOGY: not relevant
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:
- 25 Met Ala Leu Glu Gln Asn Gln Ser Thr Asp Tyr Tyr Tyr Glu Glu Asn 1 5 10 15
 - Glu Met Asn Gly Thr Tyr Asp Tyr Ser Gln Tyr Glu Leu Ile Cys Ile 20 25 30
- Lys Glu Asp Val Arg Glu Phe Ala Lys Val Phe Leu Pro Val Phe Leu 30 45

Thr Ile Ala Phe Val Ile Gly Leu Ala Gly Asn Ser Met Val Val Ala

- 28 -

*		50					55					60				
	Ile 65	Tyr	Ala	Tyr	Tyr	Lys 70	Lys	Gln	Arg	Thr	Lys 75	Thr	qaA	Val		Ile 80
5	Leu	Asn	Leu	Ala	Val 85	Ala	Asp	Leu	Leu	Leu 90	Leu	Phe	Thr	Leu	Pro 95	Phe
	Trp	Ala	Val	Asn 100	Ala	Val	His	Gly	Trp 105	Val	Leu	Gly	Lys	Ile 110	Met	Cys
	Lys	Ile	Thr 115	Ser	Ala	Leu	Tyr	Thr 120	Leu	Asn	Phe	Val	Ser 125	Gly	Met	Gln
10	Phe	Leu 130	Ala	Сув	Ile	Ser	Ile 135	Asp	Arg	Tyr	Val	Ala 140	Val	Thr	Asn	Val
	Pro 145	Ser	Gln	Ser	Gly	Val 150	Gly	Lys	Pro	Cys	Trp 155	Ile	Ile	Cys	Phe	Cys 160
15	Val	Trp	Met	Ala	Ala 165	Ile	Leu	Leu	Ser	Ile 170	Pro	Gln	Leu	Val	Phe 175	Tyr
	Thr	Val	Asn	Asp 180	Asn	Ala	Arg	Cys	Ile 185	Pro	Ile	Phe	Pro	Arg 190	Tyr	Leu
	Gly	Thr	Ser 195	Met	Lys	Ala	Leu	Ile 200	Gln	Met	Leu	Glu	11e 205	CÀa	Ile	Gly
20	Phe	Val 210	Val	Pro	Phe	Leu	Ile 215	Met	Gly	Val	Сув	Tyr 220	Phe	Ile	Thr	Ala
	Arg 225	Thr	Leu	Met	Lys	Met 230	Pro	Asn	Ile	Lys	Ile 235	Ser	Arg	Pro	Leu	Lys 240
25	Val	Leu	Leu	Thr	Val 245	Val	Ile	Val	Phe	Ile 250	Val	Thr	Gln	Leu	Pro 255	Tyr
	Asn	Ile	Val	Lys 260	Phe	Сув	Arg	Ala	Ile 265	Asp	Ile	Ile	Tyr	Ser 270	Leu	Ile
	Thr	Ser	Cys 275	Asn	Met	Ser	Lys	Arg 280	Met	Asp	Ile	Ala	Ile 285	Gln	Val	Thr
30	Glu	Ser 290	Ile	Ala	Leu	Phe	His 295	Ser	Cys	Leu	Asn	Pro 300	Ile	Leu	Tyr	Val
	Phe 305	Met	Gly	Ala	Ser	Phe 310	Lys	neA	Tyr	Val	Met 315	ГЛЗ	Val	Ala	Lys	Lys 320
35	Tyr	Gly	Ser	Trp	Arg 325	Arg	Gln	Arg	Gln	Ser 330	Val	Glu	Glu	Phe	Pro 335	Phe
	Asp	Ser	Glu	Gly 340	Pro	Thr	Glu	Pro	Thr 345	Ser	Thr	Phe	Ser	Ile 350		

- 29 -

- (24) INFORMATION FOR SEQ ID NO:23:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1116 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single(D) TOPOLOGY: linear

5

- (ii) MOLECULE TYPE: DNA (genomic)
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:
- ATGCCAGGAA ACGCCACCCC AGTGACCACC ACTGCCCCGT GGGCCTCCCCT GGGCCTCTCC 60 10 GCCAAGACCT GCAACAACGT GTCCTTCGAA GAGAGCAGGA TAGTCCTGGT CGTGGTGTAC 120 AGCGCGGTGT GCACGCTGGG GGTGCCGGCC AACTGCCTGA CTGCGTGGCT GGCGCTGCTG 180 CAGGTACTGC AGGGCAACGT GCTGGCCGTC TACCTGCTCT GCCTGGCACT CTGCGAACTG 240 CTGTACACAG GCACGCTGCC ACTCTGGGTC ATCTATATCC GCAACCAGCA CCGCTGGACC 300 CTAGGCCTGC TGGCCTCGAA GGTGACCGCC TACATCTTCT TCTGCAACAT CTACGTCAGC 360 15 ATCCTCTTCC TGTGCTGCAT CTCCTGCGAC CGCTTCGTGG CCGTGGTGTA CGCGCTGGAG 420 AGTCGGGGCC GCCGCCGC GAGGACCGCC ATCCTCATCT CCGCCTGCAT CTTCATCCTC 480 GTCGGGATCG TTCACTACCC GGTGTTCCAG ACGGAAGACA AGGAGACCTG CTTTGACATG 540 CTGCAGATGG ACAGCAGGAT TGCCGGGTAC TACTACGCCA GGTTCACCGT TGGCTTTGCC 600 ATCCCTCTCT CCATCATCGC CTTCACCAAC CACCGGATTT TCAGGAGCAT CAAGCAGAGC 660 20 ATGGGCTTAA GCGCTGCCCA GAAGGCCAAG GTGAAGCACT CGGCCATCGC GGTGGTTGTC 720 ATCTTCCTAG TCTGCTTCGC CCCGTACCAC CTGGTTCTCC TCGTCAAAGC CGCTGCCTTT 780 TCCTACTACA GAGGAGACAG GAACGCCATG TGCGGCTTGG AGGAAAGGCT GTACACAGCC 840 TCTGTGGTGT TTCTGTGCCT GTCCACGGTG AACGGCGTGG CTGACCCCAT TATCTACGTG 900 CTGGCCACGG ACCATTCCCG CCAAGAAGTG TCCAGAATCC ATAAGGGGTG GAAAGAGTGG 960 25 TCCATGAAGA CAGACGTCAC CAGGCTCACC CACAGCAGGG ACACCGAGGA GCTGCAGTCG1020 CCCGTGGCCC TTGCAGACCA CTACACCTTC TCCAGGCCCG TGCACCCACC AGGGTCACCA1080 TGCCCTGCAA AGAGGCTGAT TGAGGAGTCC TGCTGA 1116
 - (25) INFORMATION FOR SEO ID NO:24:
- (i) SEQUENCE CHARACTERISTICS:

 (A) LENGTH: 371 amino acids

. • • •

- 30 -

- (B) TYPE: amino acid
- (C) STRANDEDNESS:

- (D) TOPOLOGY: not relevant
- (ii) MOLECULE TYPE: protein
- 5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Pro Gly Asn Ala Thr Pro Val Thr Thr Thr Ala Pro Trp Ala Ser 1 5 10 15

Leu Gly Leu Ser Ala Lys Thr Cys Asn Asn Val Ser Phe Glu Glu Ser 20 25 30

10 Arg Ile Val Leu Val Val Val Tyr Ser Ala Val Cys Thr Leu Gly Val 35 40 45

Pro Ala Asn Cys Leu Thr Ala Trp Leu Ala Leu Leu Gln Val Leu Gln 50 55 60

Gly Asn Val Leu Ala Val Tyr Leu Leu Cys Leu Ala Leu Cys Glu Leu 15 65 70 75 80

Leu Tyr Thr Gly Thr Leu Pro Leu Trp Val Ile Tyr Ile Arg Asn Gln 85 90 95

His Arg Trp Thr Leu Gly Leu Leu Ala Ser Lys Val Thr Ala Tyr Ile 100 $$105\,$

20 Phe Phe Cys Asn Ile Tyr Val Ser Ile Leu Phe Leu Cys Cys Ile Ser 115 120 125

Cys Asp Arg Phe Val Ala Val Val Tyr Ala Leu Glu Ser Arg Gly Arg 130 135 140

Arg Arg Arg Arg Thr Ala Ile Leu Ile Ser Ala Cys Ile Phe Ile Leu 25 145 150 155 160

Val Gly Ile Val His Tyr Pro Val Phe Gln Thr Glu Asp Lys Glu Thr 165 170 175

Cys Phe Asp Met Leu Gln Met Asp Ser Arg Ile Ala Gly Tyr Tyr Tyr 180 185 190

30 Ala Arg Phe Thr Val Gly Phe Ala Ile Pro Leu Ser Ile Ile Ala Phe 195 200 205

Thr Asn His Arg Ile Phe Arg Ser Ile Lys Gln Ser Met Gly Leu Ser 210 215 220

Ala Ala Gln Lys Ala Lys Val Lys His Ser Ala Ile Ala Val Val Val 225 230 235 240

- 31 -

- Ile Phe Leu Val Cys Phe Ala Pro Tyr His Leu Val Leu Leu Val Lys 245 250 255
- Ala Ala Ala Phe Ser Tyr Tyr Arg Gly Asp Arg Asn Ala Met Cys Gly 260 265 270
- 5 Leu Glu Glu Arg Leu Tyr Thr Ala Ser Val Val Phe Leu Cys Leu Ser 275 280 285
 - Thr Val Asn Gly Val Ala Asp Pro Ile Ile Tyr Val Leu Ala Thr Asp 290 295 300
- His Ser Arg Gln Glu Val Ser Arg Ile His Lys Gly Trp Lys Glu Trp 10 305 310 315 320
 - Ser Met Lys Thr Asp Val Thr Arg Leu Thr His Ser Arg Asp Thr Glu
 - Glu Leu Gln Ser Pro Val Ala Leu Ala Asp His Tyr Thr Phe Ser Arg 340 345 350
- Pro Val His Pro Pro Gly Ser Pro Cys Pro Ala Lys Arg Leu Ile Glu 355 360 365

Glu Ser Cys 370

- (26) INFORMATION FOR SEQ ID NO:25:
- 20 (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1113 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

ATGGCGAACT ATAGCCATGC AGCTGACAAC ATTTTGCAAA ATCTCTCGCC TCTAACAGCC 60

TTTCTGAAAC TGACTTCCTT GGGTTTCATA ATAGGAGTCA GCGTGGTGGG CAACCTCCTG 120

ATCTCCATTT TGCTAGTGAA AGATAAGACC TTGCATAGAG CACCTTACTA CTTCCTGTTG 180

30 GATCTTTGCT GTTCAGATAT CCTCAGATCT GCAATTTGTT TCCCATTTGT GTTCAACTCT 240

GTCAAAAATG GCTCTACCTG GACTTATGGG ACTCTGACTT GCAAAGTGAT TGCCTTTCTG 300

GGGGTTTTGT CCTGTTTCCA CACTGCTTTC ATGCTCTTCT GCATCAGTGT CACCAGATAC 360

TTAGCTATCG CCCATCACCG CTTCTATACA AAGAGGCTGA CCTTTTGGAC GTGTCTGGCT 420

GTGATCTGTA TGGTGTGGAC TCTGTCTGTG GCCATGGCAT TTCCCCCGGT TTTAGACGTG 480

- 32 -

GGCACTTACT CATTCATTAG GGAGGAAGAT CAATGCACCT TCCAACACCG CTCCTTCAGG 540
GCTAATGATT CCTTAGGATT TATGCTGCTT CTTGCTCTCA TCCTCCTAGC CACACAGCTT 600
GTCTACCTCA AGCTGATATT TTTCGTCCAC GATCGAAGAA AAATGAAGCC AGTCCAGTTT 660
GTAGCAGCAG TCAGCCAGAA CTGGACTTTT CATGGTCCTG GAGCCAGTGG CCAGGCAGCT 720
5 GCCAATTGGC TAGCAGGATT TGGAAGGGGT CCCACACCAC CCACCTTGCT GGGCATCAGG 780
CAAAATGCAA ACACCACAGG CAGAAGAAGG CTATTGGTCT TAGACCGAGTT CAAAATGGAG 840
AAAAGAATCA GCAGAATGTT CTATATAATG ACTTTCTGT TTCTAACCTT GTGGGGCCCC 900
CTAACAGCTG CTGTCTGGAT GAGAGTTTTT GCAAGAGAGGC CTGTAGTACC AGGGGGATTT 960
CTAACAGCTG CTGTCTGGAT GAGTTTTTGCC CAAAGCAGCAC TCATTACTT TGTCTGCATT1020
10 TTCTCAAACA GGGAGCTGAG GCGCTGTTC AGCACAACCC TTCTTTACTG CAGAAAATCC1080
AGGTTACCAA GGGAACCTTA CTGTGTTATA TGA

(27) INFORMATION FOR SEO ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 370 amino acids
- 15 (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: not relevant
 - (ii) MOLECULE TYPE: protein
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:
- 20 Met Ala Asn Tyr Ser His Ala Ala Asp Asn Ile Leu Gln Asn Leu Ser 1 5 10 15

Pro Leu Thr Ala Phe Leu Lys Leu Thr Ser Leu Gly Phe Ile Ile Gly
20 25 30

Val Ser Val Val Gly Asn Leu Leu Ile Ser Ile Leu Leu Val Lys Asp 35 40 45

Lys Thr Leu His Arg Ala Pro Tyr Tyr Phe Leu Leu Asp Leu Cys Cys 50 55 60

Ser Asp Ile Leu Arg Ser Ala Ile Cys Phe Pro Phe Val Phe Asn Ser 65 70 75 80

Val Lys Asn Gly Ser Thr Trp Thr Tyr Gly Thr Leu Thr Cys Lys Val

Ile Ala Phe Leu Gly Val Leu Ser Cys Phe His Thr Ala Phe Met Leu

- 33 -

				100					105					110		
	Phe	Cys	Ile 115	Ser	Val	Thr	Arg	Tyr 120	Leu	Ala	Ile	Ala	His 125	His	Arg	Phe
5	Tyr	Thr 130	Lys	Arg	Leu	Thr	Phe 135	Trp	Thr	Сув	Leu	Ala 140	Val	Ile	Cys	Met
	Val 145	Trp	Thr	Leu	Ser	Val 150	Ala	Met	Ala	Phe	Pro 155	Pro	Val	Leu	qaA	Val 160
	Gly	Thr	Tyr	Ser	Phe 165	Ile	Arg	Glu	Glu	Asp 170	Gln	Сув	Thr	Phe	Gln 175	His
10	Arg	Ser	Phe	Arg 180	Ala	Asn	Asp	Ser	Leu 185	Gly	Phe	Met	Leu	Leu 190	Leu	Ala
	Leu	Ile	Leu 195	Leu	Ala	Thr	Gln	Leu 200	Val	Tyr	Leu	Lys	Leu 205	Ile	Phe	Phe
15	Val	His 210	Asp	Arg	Arg	Lys	Met 215	Lys	Pro	Val	Gln	Phe 220	Val	Ala	Ala	Val
	Ser 225	Gln	Asn	Trp	Thr	Phe 230	His	Gly	Pro	Gly	Ala 235	Ser	Gly	Gln	Ala	Ala 240
					Ala 245					250					255	
20				260	Gln				265					270		
			275		Phe			280					285			
25		290			Leu		295					300				
	Cys 305	Tyr	Trp	Arg	Val	Phe 310	Ala	Arg	Gly	Pro	Val 315	Val	Pro	Gly	Gly	Phe 320
					Val 325					330			_		335	
30				340	Phe				345					350		
	Thr	Leu	Leu 355	Tyr	Cys	Arg	Lys	Ser 360	Arg	Leu	Pro	Arg	Glu 365	Pro	Tyr	Cya
35	Val	11e 370														

(28) INFORMATION FOR SEQ ID NO:27:

- 34 -

(i) SEQUENCE CHARACTERISTICS:

5

- (A) LENGTH: 1080 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

ATGCAGGTCC CGAACAGCAC CGGCCCGGAC AACGCGACGC TGCAGATGCT GCGGAACCCG 60 GCGATCGCGG TGGCCCTGCC CGTGGTGTAC TCGCTGGTGG CGGCGGTCAG CATCCCGGGC 120 10 AACCTCTTCT CTCTGTGGGT GCTGTGCCGG CGCATGGGGC CCAGATCCCC GTCGGTCATC 180 TTCATGATCA ACCTGAGCGT CACGGACCTG ATGCTGGCCA GCGTGTTGCC TTTCCAAATC 240 TACTACCATT GCAACCGCCA CCACTGGGTA TTCGGGGTGC TGCTTTGCAA CGTGGTGACC 300 GTGGCCTTTT ACGCAAACAT GTATTCCAGC ATCCTCACCA TGACCTGTAT CAGCGTGGAG 360 CGCTTCCTGG GGGTCCTGTA CCCGCTCAGC TCCAAGCGCT GGCGCCGCCG TCGTTACGCG 420 15 GTGGCCGCGT GTGCAGGGAC CTGGCTGCTG CTCCTGACCG CCCTGTGCCC GCTGGCGCGC 480 ACCGATCTCA CCTACCCGGT GCACGCCCTG GGCATCATCA CCTGCTTCGA CGTCCTCAAG 540 TGGACGATGC TCCCCAGCGT GGCCATGTGG GCCGTGTTCC TCTTCACCAT CTTCATCCTG 600 CTGTTCCTCA TCCCGTTCGT GATCACCGTG GCTTGTTACA CGGCCACCAT CCTCAAGCTG 660 TTGCGCACGG AGGAGGCGCA CGGCCGGGAG CAGCGGAGGC GCGCGGTGGG CCTGGCCGCG 720 20 GTGGTCTTGC TGGCCTTTGT CACCTGCTTC GCCCCCAACA ACTTCGTGCT CCTGGCGCAC 780 ATCGTGAGCC GCCTGTTCTA CGGCAAGAGC TACTACCACG TGTACAAGCT CACGCTGTGT 840 CTCAGCTGCC TCAACAACTG TCTGGACCCG TTTGTTTATT ACTTTGCGTC CCGGGAATTC 900 CAGCTGCGCC TGCGGGAATA TTTGGGCTGC CGCCGGGTGC CCAGAGACAC CCTGGACACG 960 CGCCGCGAGA GCCTCTTCTC CGCCAGGACC ACGTCCGTGC GCTCCGAGGC CGGTGCGCAC1020 25 CCTGAAGGGA TGGAGGGAGC CACCAGGCCC GGCCTCCAGA GGCAGGAGAG TGTGTTCTGA1080

- (29) INFORMATION FOR SEQ ID NO:28:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 359 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:

30

(D) TOPOLOGY: not relevant

- 35 -

(ii) MOLECULE TYPE: protein

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Gln Val Pro Asn Ser Thr Gly Pro Asp Asn Ala Thr Leu Gln Met

1 10 15

5 Leu Arg Asn Pro Ala Ile Ala Val Ala Leu Pro Val Val Tyr Ser Leu 20 25 30

Val Ala Ala Val Ser Ile Pro Gly Asn Leu Phe Ser Leu Trp Val Leu 35 40 45

Cys Arg Arg Met Gly Pro Arg Ser Pro Ser Val Ile Phe Met Ile Asn 50 55 60

Leu Ser Val Thr Asp Leu Met Leu Ala Ser Val Leu Pro Phe Gln Ile 65 70 75 80

Tyr Tyr His Cys Asn Arg His His Trp Val Phe Gly Val Leu Leu Cys 85 90 95

Asn Val Val Thr Val Ala Phe Tyr Ala Asn Met Tyr Ser Ser Ile Leu 100 105 110

Thr Met Thr Cys Ile Ser Val Glu Arg Phe Leu Gly Val Leu Tyr Pro 115 120 125

Leu Ser Ser Lys Arg Trp Arg Arg Arg Tyr Ala Val Ala Ala Cys
20 130 135 140

Ala Gly Thr Trp Leu Leu Leu Leu Thr Ala Leu Cys Pro Leu Ala Arg 145 150 155 160

Thr Asp Leu Thr Tyr Pro Val His Ala Leu Gly Ile Ile Thr Cys Phe 165 170 175

Asp Val Leu Lys Trp Thr Met Leu Pro Ser Val Ala Met Trp Ala Val

Phe Leu Phe Thr Ile Phe Ile Leu Leu Phe Leu Ile Pro Phe Val Ile
195 200 205

Thr Val Ala Cys Tyr Thr Ala Thr Ile Leu Lys Leu Leu Arg Thr Glu 30 210 215 220

> Glu Ala His Gly Arg Glu Gln Arg Arg Arg Ala Val Gly Leu Ala Ala 225 230 235 240

> Val Val Leu Leu Ala Phe Val Thr Cys Phe Ala Pro Asn Asn Phe Val 245 250 255

Leu Leu Ala His Ile Val Ser Arg Leu Phe Tyr Gly Lys Ser Tyr Tyr 260 265 270

- 36 -

His Val Tyr Lys Leu Thr Leu Cys Leu Ser Cys Leu Asn Asn Cys Leu 275 280 285

Asp Pro Phe Val Tyr Tyr Phe Ala Ser Arg Glu Phe Gln Leu Arg Leu 290 295 300

5 Arg Glu Tyr Leu Gly Cys Arg Arg Val Pro Arg Asp Thr Leu Asp Thr 305 310 315 320

Arg Arg Glu Ser Leu Phe Ser Ala Arg Thr Thr Ser Val Arg Ser Glu
325 330 335

Ala Gly Ala His Pro Glu Gly Met Glu Gly Ala Thr Arg Pro Gly Leu 10 340 345 350

Gln Arg Gln Glu Ser Val Phe 355

(30) INFORMATION FOR SEQ ID NO:29:

15

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1503 base pairs

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

ATGGAGCGTC CCTGGGAGGA CAGCCCAGGC CCGGAGGGGG CAGCTGAGGG CTCGCCTGTG 60

CCAGTCGCCG CCGGGGCGC CTCCGGTGCC GCGGCGAGTG GCACAGGCTG GCAGCCATGG 120

GCTGAGTGCC CGGGACCCAA GGGGAGGGGG CAACTGCTGG CGACCGCCG CCCTTTGCGT 180

CGCTGGCCCG CCCCCTCGCC TGCCAGCTCC AGCCCCGCCC CCGGAGCGGC GTCCGCTCAC 240

25 TCGGTTCAAG GCAGCGCGAC TGCGGGTGC GCACGACCAG GGCGCAGACC TTGGGGCGCG 300

CGGCCCATGG AGTCGGGGCT GCTGCGGCCG GCGCCGGTGA GCGAGGCCT TGGGGCGCG 420

GACGCCGTGG TGTGCCTGGC GGTGTGCGC TTCATCGTGC TAGAGAATCT AGCCGTGTG 480

TTGGTGCTCG GACGCCACCC GCGCTTCCAC GCTCCCATGT TCCTGCTCCT GGGCAGCCT 540

30 ACGTTGTCGG ATCTGCTGGC AGGCGCGCC TACGCCGCA ACATCCTACT GTCGGGCCG 600

CTCACGCTGA AACTGTCCCC CGCGCTCTGG TTCGCACGGG AGGGAGGCGT CTTCGTGGCA 660

CTCACTGCGT CCGTGCTGAG CCTCCTGGCC ATCGCGCGG AGGCAGCCT CACCATGGCG 720

- 37 -

CGCAGGGGGC CCGCCCCGT CTCCAGTCGG GGGCGCACGC TGGCGATGGC AGCCGCGGCC 780
TGGGGCGTGT CGCTGCTCCT CGGGCTCCTG CCAGCGCTGG GCTGGAATTG CCTGGGTCGC 840
CTGGACGCTT GCTCCACTGT CTTGCCGCTC TACGCCAAGG CCTACGTGCT CTTCTGCGTG 900
CTCGCCTTCG TGGGCATCCT GGCCGCGATC TGTGCACTCT ACGCGCGCAT CTACTGCCAG 960
5 GTACGCGCCA ACGCGCGGC CCTGCCGGCA CGGCCCGGGA CTGCGGGGAC CACCTCGACC1020
CGGGCGCGCT GCAAGCCGCG CTCTCTGGCC TTGCTGCGCA CGCTCAGCGT GGTGCTCCTG1080
GCCTTTGTGG CATGTTGGGG CCCCCTCTTC CTGCTGCTG TGCTCGACGT GGCGTGCCCG1140
GCGCGCACCT GTCCTGTACT CCTGCAGGCC GATCCCTTCC TGGGACTGGC CATGGCCAAC1200
TCACTTCTGA ACCCCATCAT CTACACGCTC ACCAACCGCG ACCTGCGCCA CGCGCTCCTG1260
10 CGCCTGGTCT GCTGCGGACG CCACTCCTGC GGCAGAGACC CGAGTGGCTC CCAGCAGTCG1320
GCGAGCGCGG CTGAGGCTTC CGGGGGCCTG CGCCGCTGCC TGCCCCGGG CCTTGATGGG1380
AGCTTCAGCG GCTCGGAGCG CTCATCGCCC CAGCGCGACC GGCTGGACAC CAGCGGCTCC1440
ACAGGCAGCC CCGGTGCACC CACAGCCGC CGGACTCTGG GGCTGCAGAC1500
TGA

- 15 (31) INFORMATION FOR SEQ ID NO:30:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 500 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
- 20 (D) TOPOLOGY: not relevant
 - (ii) MOLECULE TYPE: protein
 - (\times i) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Glu Arg Pro Trp Glu Asp Ser Pro Gly Pro Glu Gly Ala Ala Glu
1 5 10 15

25 Gly Ser Pro Val Pro Val Ala Ala Gly Ala Arg Ser Gly Ala Ala Ala 20 25 30

Ser Gly Thr Gly Trp Gln Pro Trp Ala Glu Cys Pro Gly Pro Lys Gly 35 40 45

> Pro Ser Pro Ala Ser Ser Ser Pro Ala Pro Gly Ala Ala Ser Ala His 65 70 75 80

- 38 -

	Ser	Val	Gln	Gly	Ser 85	Ala	Thr	Ala	Gly	Gly 90	Ala	Arg	Pro	Gly	Arg 95	Arg
	Pro	Trp	Gly	Ala 100	Arg	Pro	Met	Glu	Ser 105		Leu	Leu	Arg	Pro 110	Ala	Pro
5	Val	Ser	Glu 115	Val	Ile	Val	Leu	His 120	Tyr	Asn	Tyr	Thr	Gly 125	Lys	Leu	Arg
	Gly	Ala 130	Ser	Tyr	Gln	Pro	Gly 135	Ala	Gly	Leu	Arg	Ala 140	Asp	Ala	Val	Val
10	Cys 145	Leu	Ala	Val	Cys	Ala 150	Phe	Ile	Val	Leu	Glu 155	Asn	Leu	Ala	Val	Leu 160
	Leu	Val	Leu	Gly	Arg 165	His	Pro	Arg	Phe	His 170	Ala	Pro	Met	Phe	Leu 175	Leu
	Leu	Gly	Ser	Leu 180	Thr	Leu	Ser	Asp	Leu 185	Leu	Ala	Gly	Ala	Ala 190	Tyr	Ala
15	Ala	Asn	Ile 195	Leu	Leu	Ser	Gly	Pro 200	Leu	Thr	Leu	Lys	Leu 205	Ser	Pro	Ala
	Leu	Trp 210	Phe	Ala	Arg	Glu	Gly 215	Gly	Val	Phe	Val	Ala 220	Leu	Thr	Ala	Ser
20	Val 225	Leu	Ser	Leu	Leu	Ala 230	Ile	Ala	Leu	Glu	Arg 235	Ser	Leu	Thr	Met	Ala 240
	Arg	Arg	Gly	Pro	Ala 245	Pro	Val	Ser	Ser	Arg 250	Gly	Arg	Thr	Leu	Ala 255	Met
	Ala	Ala	Ala	Ala 260	Trp	Gly	Val	Ser	Leu 265	Leu	Leu	Gly	Leu	Leu 270	Pro	Ala
25	Leu	Gly	Trp 275	Asn	Суз	Leu	Gly	Arg 280	Leu	Asp	Ala	Сув	Ser 285	Thr	Val	Leu
		290					295				_	300			Phe	
30	305					310					315				Cya	320
	Val	Arg	Ala	Asn	Ala 325	Arg	Arg	Leu	Pro	Ala 330	Arg	Pro	Gly	Thr	Ala 335	Gly
				340					345					350	Leu	
35			355					360					365		Gly	
	Leu	Phe	Leu	Leu	Leu	Leu	Leu	Asp	Val	Ala	Cys	Pro	Ala	Arg	Thr	Суз

WO 00/31258 PCT/US99/23687 ·

- 39 -

370 375 380

Pro Val Leu Leu Gln Ala Asp Pro Phe Leu Gly Leu Ala Met Ala Asn 385 390 590 595 400

Ser Leu Leu Asn Pro Ile Ile Tyr Thr Leu Thr Asn Arg Asp Leu Arg 405 410 415

His Ala Leu Leu Arg Leu Val Cys Cys Gly Arg His Ser Cys Gly Arg
420 425 430

Asp Pro Ser Gly Ser Gln Gln Ser Ala Ser Ala Ala Glu Ala Ser Gly
435 440 445

10 Gly Leu Arg Arg Cys Leu Pro Pro Gly Leu Asp Gly Ser Phe Ser Gly 450 455 460

 Ser Glu Arg Ser Ser Pro Gln Arg Asp Gly Leu Asp Thr Ser Gly Ser

 465
 470
 475
 480

Thr Gly Ser Pro Gly Ala Pro Thr Ala Ala Arg Thr Leu Val Ser Glu 15 495 490 495

Pro Ala Ala Asp 500

20

- (32) INFORMATION FOR SEQ ID NO:31:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1029 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
- 25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

ATGCAAGCCG TCGACAATCT CACCTCTGCG CCTGGGAACA CCAGTCTGTG CACCAGAGAC 60

TACAAAATCA CCCAGGTCCT CTTCCCACTG CTCTACACTG TCCTGTTTT TGTTGGACTT 120

ATCACAAATG GCCTGGCGAT GAGGATTTTC TTTCAAATCC GGAGTAAATC AAACTTTATT 180

ATTTTTCTTA AGAACACAGT CATTTCTGAT CTTCTCATGA TTCTGACTTT TCCATTCAAA 240

30 ATTCTTAGTG ATGCCAAACT GGGAACAGGA CCACTGAGAA CTTTTGTGTG TCAAGTTACC 300

TCCGTCATAT TTTATTTCAC AATGTATATC AGTATTTCAT TCCTGGGACT GATAACTATC 360

GATCGCTACC AGAAGACCAC CAGGCCATTT AAAACATCCA ACCCCAAAAA TCTCTTGGGG 420

GCTAAGATTC TCTCTGTTGT CATCTGGGCA TTCATGTTCT TACTCTCTTT GCCTAACATG 480

WO 00/31258

- 40 -

PCT/US99/23687

ATTCTGACCA ACAGGCAGCC GAGAGACAAG AATGTGAAGA AATGCTCTTT CCTTAAATCA 540 GAGTTCGGTC TAGTCTGGCA TGAAATAGTA AATTACATCT GTCAAGTCAT TTTCTGGATT 600 AATTTCTTAA TTGTTATTGT ATGTTATACA CTCATTACAA AAGAACTGTA CCGGTCATAC 660 GTAAGAACGA GGGGTGTAGG TAAAGTCCCC AGGAAAAAGG TGAACGTCAA AGTTTTCATT 720 5 ATCATTGCTG TATTCTTTAT TTGTTTTGTT CCTTTCCATT TTGCCCGAAT TCCTTACACC 780 CTGAGCCAAA CCCGGGATGT CTTTGACTGC ACTGCTGAAA ATACTCTGTT CTATGTGAAA 840 GAGAGCACTC TGTGGTTAAC TTCCTTAAAT GCATGCCTGG ATCCGTTCAT CTATTTTTTC 900 CTTTGCAAGT CCTTCAGAAA TTCCTTGATA AGTATGCTGA AGTGCCCCAA TTCTGCAACA 960 TCTCTGTCCC AGGACAATAG GAAAAAAGAA CAGGATGGTG GTGACCCAAA TGAAGAGACT1020 10 CCAATGTAA 1029

- (33) INFORMATION FOR SEQ ID NO:32:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 342 amino acids
 - (B) TYPE: amino acid
- 15
- (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:
- Met Gln Ala Val Asp Asn Leu Thr Ser Ala Pro Gly Asn Thr Ser Leu 20
 - Cys Thr Arg Asp Tyr Lys Ile Thr Gln Val Leu Phe Pro Leu Leu Tyr
 - Thr Val Leu Phe Phe Val Gly Leu Ile Thr Asn Gly Leu Ala Met Arg
- 25 Ile Phe Phe Gln Ile Arg Ser Lys Ser Asn Phe Ile Ile Phe Leu Lys
 - Asn Thr Val Ile Ser Asp Leu Leu Met Ile Leu Thr Phe Pro Phe Lys
- Ile Leu Ser Asp Ala Lys Leu Gly Thr Gly Pro Leu Arg Thr Phe Val 30
 - Cys Gln Val Thr Ser Val Ile Phe Tyr Phe Thr Met Tyr Ile Ser Ile 105
 - Ser Phe Leu Gly Leu Ile Thr Ile Asp Arg Tyr Gln Lys Thr Thr Arg

- 41 -

120 125 Pro Phe Lys Thr Ser Asn Pro Lys Asn Leu Leu Gly Ala Lys Ile Leu 135 Ser Val Val Ile Trp Ala Phe Met Phe Leu Leu Ser Leu Pro Asn Met 5 150 155 Ile Leu Thr Asn Arg Gln Pro Arg Asp Lys Asn Val Lys Lys Cys Ser Phe Leu Lys Ser Glu Phe Gly Leu Val Trp His Glu Ile Val Asn Tyr 10 Ile Cys Gln Val Ile Phe Trp Ile Asn Phe Leu Ile Val Ile Val Cys 200 Tyr Thr Leu Ile Thr Lys Glu Leu Tyr Arg Ser Tyr Val Arg Thr Arg 215 Gly Val Gly Lys Val Pro Arg Lys Lys Val Asn Val Lys Val Phe Ile 15 235 Ile Ile Ala Val Phe Phe Ile Cys Phe Val Pro Phe His Phe Ala Arg 250 Ile Pro Tyr Thr Leu Ser Gln Thr Arg Asp Val Phe Asp Cys Thr Ala 265 20 Glu Asn Thr Leu Phe Tyr Val Lys Glu Ser Thr Leu Trp Leu Thr Ser 280 Leu Asn Ala Cys Leu Asp Pro Phe Ile Tyr Phe Phe Leu Cys Lys Ser Phe Arg Asn Ser Leu Ile Ser Met Leu Lys Cys Pro Asn Ser Ala Thr 25 Ser Leu Ser Gln Asp Asn Arg Lys Lys Glu Gln Asp Gly Gly Asp Pro Asn Glu Glu Thr Pro Met 340 30 (34) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1077 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
- 35 (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)

WO 00/31258

PCT/US99/23687

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

ATGTCGGTCT GCTACCGTCC CCCAGGGAAC GAGACACTGC TGAGCTGGAA GACTTCGCGG 60 GCCACAGGCA CAGCCTTCCT GCTGCTGGCG GCGCTGCTGG GGCTGCCTGG CAACGGCTTC 120 GTGGTGTGGA GCTTGGCGGG CTGGCGGCCT GCACGGGGG GACCGCTGGC GGCCACGCTT 180 5 GTGCTGCACC TGGCGCTGGC CGACGGCGCG GTGCTGCTGC TCACGCCGCT CTTTGTGGCC 240 TTCCTGACCC GGCAGGCCTG GCCGCTGGGC CAGGCGGGCT GCAAGGCGGT GTACTACGTG 300 TGCGCGCTCA GCATGTACGC CAGCGTGCTG CTCACCGGCC TGCTCAGCCT GCAGCGCTGC 360 CTCGCAGTCA CCCGCCCCTT CCTGGCGCCT CGGCTGCGCA GCCCGGCCCT GGCCCGCCGC 420 CTGCTGCTGG CGGTCTGGCT GGCCGCCCTG TTGCTCGCCG TCCCGGCCGC CGTCTACCGC 480 10 CACCTGTGGA GGGACCGCGT ATGCCAGCTG TGCCACCCGT CGCCGGTCCA CGCCGCCGCC 540 CACCTGAGCC TGGAGACTCT GACCGCTTTC GTGCTTCCTT TCGGGCTGAT GCTCGGCTGC 600 TACAGCGTGA CGCTGGCACG GCTGCGGGGC GCCCGCTGGG GCTCCGGGCG GCACGGGGCG 660 CGGGTGGGCC GGCTGGTGAG CGCCATCGTG CTTGCCTTCG GCTTGCTCTG GGCCCCCTAC 720 CACGCAGTCA ACCTTCTGCA GGCGGTCGCA GCGCTGGCTC CACCGGAAGG GGCCTTGGCG 780 15 AAGCTGGGCG GAGCCGGCCA GGCGGCGCGA GCGGGAACTA CGGCCTTGGC CTTCTTCAGT 840 TCTAGCGTCA ACCCGGTGCT CTACGTCTTC ACCGCTGGAG ATCTGCTGCC CCGGGCAGGT 900 CCCCGTTTCC TCACGCGGCT CTTCGAAGGC TCTGGGGAGG CCCGAGGGGG CGGCCGCTCT 960 AGGGAAGGGA CCATGGAGCT CCGAACTACC CCTCAGCTGA AAGTGGTGGG GCAGGGCCGC1020 GGCAATGGAG ACCCGGGGGG TGGGATGGAG AAGGACGGTC CGGAATGGGA CCTTTGA 1077 20 (35) INFORMATION FOR SEQ ID NO:34:

- 42 - -

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 358 amino acids
 - (B) TYPE: amino acid
- (C) STRANDEDNESS:
- 25 (D) TOPOLOGY: not relevant
 - (ii) MOLECULE TYPE: protein
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Met Ser Val Cys Tyr Arg Pro Pro Gly Asn Glu Thr Leu Leu Ser Trp 1 5 . 10 15

30 Lys Thr Ser Arg Ala Thr Gly Thr Ala Phe Leu Leu Leu Ala Ala Leu

				20					25					30		
	Leu	Gly	Leu 35	Pro	Gly	Asn	Gly	Phe 40	val	. Val	. Trp	Ser	Leu 45	a Ala	Gly	/ Tr
5	Arg	Pro 50	Ala	Arg	Gly	Arg	Pro 55	Lev	Ala	Ala	Thr	Leu 60	Val	. Let	ı His	Le
	Ala 65	Leu	Ala	Asp	Gly	Ala 70	Val	Leu	Leu	Leu	Thr 75	Pro	Lev	Phe	val	Al:
	Phe	Leu	Thr	Arg	Gln 85	Ala	Trp	Pro	Leu	Gly 90	Gln	Ala	Gly	Cys	Lys 95	Al:
10	Val	Tyr	Tyr	Val 100	Cys	Ala	Leu	Ser	Met 105		Ala	Ser	Val	Leu 110		Th
	Gly	Leu	Leu 115	Ser	Leu	Gln	Arg	Суя 120	Leu	Ala	Val	Thr	Arg 125		Phe	Let
15	Ala	Pro 130	Arg	Leu	Arg	Ser	Pro 135	Ala	Leu	Ala	Arg	Arg 140		Leu	Leu	Ala
	Val 145	Trp	Leu	Ala	Ala	Leu 150	Leu	Leu	Ala	Val	Pro 155	Ala	Ala	Val	Tyr	Arg
	His	Leu	Trp	Arg	Asp 165	Arg	Val	Cys	Gln	Leu 170	Сув	His	Pro	Ser	Pro 175	Val
20	His	Ala	Ala	Ala 180	His	Leu	Ser	Leu	Glu 185	Thr	Leu	Thr	Ala	Phe 190	Val	Leu
	Pro	Phe	Gly 195	Leu	Met	Leu	Gly	Cys 200	Tyr	Ser	Val	Thr	Leu 205	Ala	Arg	Leu
25	Arg	Gly 210	Ala	Arg	Trp	Gly	Ser 215	Gly	Arg	His	Gly	Ala 220	Arg	Val	Gly	Arg
	Leu 225	Val	Ser	Ala	Ile	Val 230	Leu	Ala	Phe	Gly	Leu 235	Leu	Trp	Ala	Pro	Tyr 240
	His	Ala	Val	Asn	Leu 245	Leu	Gln	Ala	Val	Ala 250	Ala	Leu	Ala	Pro	Pro 255	Glu
30	Gly	Ala	Leu	Ala 260	Lys	Leu	Gly	Gly	Ala 265	Gly	Gln	Ala	Ala	Arg 270	Ala	Gly
	Thr	Thr	Ala 275	Leu	Ala	Phe	Phe	Ser 280	Ser	Ser	Val	Asn	Pro 285	Val	Leu	туг
35	Val	Phe 290	Thr	Ala	Gly	Asp	Leu 295	Leu	Pro	Arg	Ala	Gly 300	Pro	Arg	Phe	Leu
	Thr 305	Arg	Leu	Phe	Glu	Gly 310	Ser	Gly	Glu	Ala	Arg 315	Gly	Gly	Gly	Arg	Ser 320

- 44 -

Arg Glu Gly Thr Met Glu Leu Arg Thr Thr Pro Gln Leu Lys Val Val 325 330 335

Gly Gln Gly Arg Gly Asn Gly Asp Pro Gly Gly Gly Met Glu Lys Asp 340 345 350

- 5 Gly Pro Glu Trp Asp Leu 355
- (36) INFORMATION FOR SEQ ID NO:35:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1005 base pairs
- 10 (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:
- 15 ATGCTGGGGA TCATGGCATG GAATGCAACT TGCAAAAACT GGCTGGCAGC AGAGGCTGCC 60 CTGGAAAAGT ACTACCTTTC CATTTTTAT GGGATTGAGT TCGTTGTGGG AGTCCTTGGA 120 AATACCATTG TTGTTTACGG CTACATCTTC TCTCTGAAGA ACTGGAACAG CAGTAATATT 180 TATCTCTTTA ACCTCTGT CTCTGACTTA GCTTTTCTGT GCACCCTCCC CATGCTGATA 240 AGGAGTTATG CCAATGGAAA CTGGATATAT GGAGACGTGC TCTGCATAAG CAACCGATAT 300 20 GTGCTTCATG CCAACCTCTA TACCAGCATT CTCTTTCTCA CTTTTATCAG CATAGATCGA 360 TACTTGATAA TTAAGTATCC TTTCCGAGAA CACCTTCTGC AAAAGAAAGA GTTTGCTATT 420 TTAATCTCCT TGGCCATTTG GGTTTTAGTA ACCTTAGAGT TACTACCCAT ACTTCCCCTT 480 ATAAATCCTG TTATAACTGA CAATGGCACC ACCTGTAATG ATTTTGCAAG TTCTGGAGAC 540 CCCAACTACA ACCTCATTTA CAGCATGTGT CTAACACTGT TGGGGTTCCT TATTCCTCTT 600 25 TTTGTGATGT GTTTCTTTTA TTACAAGATT GCTCTCTTCC TAAAGCAGAG GAATAGGCAG 660 GTTGCTACTG CTCTGCCCCT TGAAAAGCCT CTCAACTTGG TCATCATGGC AGTGGTAATC 720 TTCTCTGTGC TTTTTACACC CTATCACGTC ATGCGGAATG TGAGGATCGC TTCACGCCTG 780 GGGAGTTGGA AGCAGTATCA GTGCACTCAG GTCGTCATCA ACTCCTTTTA CATTGTGACA 840 CGGCCTTTGG CCTTTCTGAA CAGTGTCATC AACCCTGTCT TCTATTTTCT TTTGGGAGAT 900 30 CACTTCAGGG ACATGCTGAT GAATCAACTG AGACACAACT TCAAATCCCT TACATCCTTT 960 AGCAGATGGG CTCATGAACT CCTACTTTCA TTCAGAGAAA AGTGA 1005

- 45 -

(37)	INFORMATION	FOR	SEQ	ID	NO:36:
------	-------------	-----	-----	----	--------

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 334 amino acids
 - (B) TYPE: amino acid
- (C) STRANDEDNESS:

5

- (D) TOPOLOGY: not relevant
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:
- Met Leu Gly Ile Met Ala Trp Asn Ala Thr Cys Lys Asn Trp Leu Ala 10 1 5 10 10 15
 - Ala Glu Ala Ala Leu Glu Lys Tyr Tyr Leu Ser Ile Phe Tyr Gly Ile
 20 25 30
 - Glu Phe Val Val Gly Val Leu Gly Asn Thr Ile Val Val Tyr Gly Tyr 35 40 45
- 15 Ile Phe Ser Leu Lys Asn Trp Asn Ser Ser Asn Ile Tyr Leu Phe Asn 50 55 60
 - Leu Ser Val Ser Asp Leu Ala Phe Leu Cys Thr Leu Pro Met Leu Ile 65 70 75 80
- Arg Ser Tyr Ala Asn Gly Asn Trp Ile Tyr Gly Asp Val Leu Cys Ile 20 85 90 95
 - Ser Asn Arg Tyr Val Leu His Ala Asn Leu Tyr Thr Ser Ile Leu Phe 100 105 110
 - Leu Thr Phe Ile Ser Ile Asp Arg Tyr Leu Ile Ile Lys Tyr Pro Phe 115 120 125
- 25 Arg Glu His Leu Leu Gln Lys Lys Glu Phe Ala Ile Leu Ile Ser Leu 130 135 140
 - Ala Ile Trp Val Leu Val Thr Leu Glu Leu Leu Pro Ile Leu Pro Leu 145 150 150 160
- Ile Asn Pro Val Ile Thr Asp Asn Gly Thr Thr Cys Asn Asp Phe Ala 30 165 170 175
 - Ser Ser Gly Asp Pro Asn Tyr Asn Leu Ile Tyr Ser Met Cys Leu Thr 180 185 190
 - Leu Leu Gly Phe Leu Ile Pro Leu Phe Val Met Cys Phe Phe Tyr Tyr
 195 200 205
- Lys Ile Ala Leu Phe Leu Lys Gln Arg Asn Arg Gln Val Ala Thr Ala 210 215 220

- 46 -

- Leu Pro Leu Glu Lys Pro Leu Asn Leu Val Ile Met Ala Val Val Ile 225 230 235 240
- Phe Ser Val Leu Phe Thr Pro Tyr His Val Met Arg Asn Val Arg Ile 245 250 255
- 5 Ala Ser Arg Leu Gly Ser Trp Lys Gln Tyr Gln Cys Thr Gln Val Val 260 265 270
 - Ile Asn Ser Phe Tyr Ile Val Thr Arg Pro Leu Ala Phe Leu Asn Ser 275 280 285
- Val Ile Asn Pro Val Phe Tyr Phe Leu Leu Gly Asp His Phe Arg Asp 10 290 295 300
 - Met Leu Met Asn Gln Leu Arg His Asn Phe Lys Ser Leu Thr Ser Phe 305 310 315 320
 - Ser Arg Trp Ala His Glu Leu Leu Leu Ser Phe Arg Glu Lys 325 330
- 15 (38) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1296 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
- 20 (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:
- ATGCAGGGG TTAACATTAC CCCGGAGCAG TTCTCTCGGC TGCTGCGGGA CCACAACCTG 60

 ACGCGGAGC AGTTCATCGC TCTGTACCGG CTGCGACCGC TCGTCTACAC CCCAGAGCTG 120

 25 CCGGGACGCG CCAAGCTGGC CCTCGTGCTC ACCGGCGTGC TCATCTTCGC CCTGGCGCTC 180

 TTTGGCAATG CTCTGGTGTT CTACGTGGTG ACCCGCAGCA AGGCCATGCG CACCGTCACC 240

 AACATCTTTA TCTGCTCCTT GGCGCTCAGT GACCTGCTCA TCACCTTCTT CTGCATTCCC 300

 GTCACCATGC TCCAGAACAT TTCCGACAAC TGGCTGGGG GTGCTTTCAT TTGCAAGATG 360

 GTGCCATTTG TCCAGTCTAC CGCTGTTGTG ACAGAAATGC TCACCTATGAC CTGCATTGCT 420

 30 GTGGAAAGGC ACCAGGGACT TGTGCATCCT TTTAAAATGA AGTGGCAATA CACCAACCGA 480

 AGGGCTTTCA CAATGCTAGG TGTGGTCTGG CTGGTGGCAG TCATCGTAGG ATCACCCATG 540

 TGGCACGTGC AACACTTGA GATCAAATAT GACTTCCTAT ATGAAAAGGA ACACATCTGC 600

TGCTTAGAAG AGTGGACCAG CCCTGTGCAC CAGAAGATCT ACACCACCTT CATCCTTGTC 660

ATCCTCTTCC TCCTGCCTCT TATGGTGATG CTTATTCTGT ACAGTAAAAT TGGTTATGAA 720 CTTTGGATAA AGAAAAGAGT TGGGGATGGT TCAGTGCTTC GAACTATTCA TGGAAAAGAA 780 ATGTCCAAAA TAGCCAGGAA GAAGAAACGA GCTGTCATTA TGATGGTGAC AGTGGTGGCT 840 CTCTTTGCTG TGTGCTGGGC ACCATTCCAT GTTGTCCATA TGATGATTGA ATACAGTAAT 900 5 TTTGAAAAGG AATATGATGA TGTCACAATC AAGATGATTT TTGCTATCGT GCAAATTATT 960 GGATTTTCCA ACTCCATCTG TAATCCCATT GTCTATGCAT TTATGAATGA AAACTTCAAA1020 AAAAATGTTT TGTCTGCAGT TTGTTATTGC ATAGTAAATA AAACCTTCTC TCCAGCACAA1080 AGGCATGGAA ATTCAGGAAT TACAATGATG CGGAAGAAAG CAAAGTTTTC CCTCAGAGAG1140 AATCCAGTGG AGGAAACCAA AGGAGAAGCA TTCAGTGATG GCAACATTGA AGTCAAATTG1200 10 TGTGAACAGA CAGAGGAGAA GAAAAAGCTC AAACGACATC TTGCTCTCTT TAGGTCTGAA1260 CTGGCTGAGA ATTCTCCTTT AGACAGTGGG CATTAA 1296

(39) INFORMATION FOR SEQ ID NO:38:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 431 amino acids
- (B) TYPE: amino acid (C) STRANDEDNESS:
- - (D) TOPOLOGY: not relevant
 - (ii) MOLECULE TYPE: protein
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:
- Met Gln Ala Leu Asn Ile Thr Pro Glu Gln Phe Ser Arg Leu Leu Arg 20
 - Asp His Asn Leu Thr Arg Glu Gln Phe Ile Ala Leu Tyr Arg Leu Arg
- Pro Leu Val Tyr Thr Pro Glu Leu Pro Gly Arg Ala Lys Leu Ala Leu 25
 - Val Leu Thr Gly Val Leu Ile Phe Ala Leu Ala Leu Phe Gly Asn Ala
 - Leu Val Phe Tyr Val Val Thr Arg Ser Lys Ala Met Arg Thr Val Thr
- 30 Asn Ile Phe Ile Cys Ser Leu Ala Leu Ser Asp Leu Leu Ile Thr Phe 90
 - Phe Cys Ile Pro Val Thr Met Leu Gln Asn Ile Ser Asp Asn Trp Leu

- 48 -

				100					105					110		
	Gly	Gly	Ala 115	Phe	Ile	Cys	Lys	Met 120	Val	Pro	Phe	Val	Gln 125	Ser	Thr	Ala
5	Val	Val 130	Thr	Glu	Met	Leu	Thr 135	Met	Thr	Cys	Ile	Ala 140	Val	Glu	Arg	His
	Gln 145	Gly	Leu	Val	His	Pro 150	Phe	Lys	Met	Lys	Trp 155	Gln	Tyr	Thr	Asn	Arg 160
	Arg	Ala	Phe	Thr	Met 165	Leu	Gly	Val	Val	Trp 170	Leu	Val	Ala	Val	Ile 175	Val
10	Gly	Ser	Pro	Met 180	Trp	His	Val	Gln	Gln 185	Leu	Glu	Ile	Lys	Tyr 190	Asp	Phe
	Leu	Tyr	Glu 195	Lys	Glu	His	Ile	Cys 200	Cys	Leu	Glu	Glu	Trp 205	Thr	Ser	Pro
15	Val	His 210	Gln	Lys	Ile	Tyr	Thr 215	Thr	Phe	Ile	Leu	Val 220	Ile	Leu	Phe	Leu
	Leu 225	Pro	Leu	Met	Val	Met 230	Leu	Ile	Leu	Tyr	Ser 235	Lys	Ile	Gly	Tyr	Glu 240
	Leu	Trp	Ile	Lys	Lys 245	Arg	Val	Gly	Asp	Gly 250	Ser	Val	Leu	Arg	Thr 255	Ile
20	His	Gly	Lys	Glu 260	Met	Ser	Lys	Ile	Ala 265	Arg	Lys	Lys	Lys	Arg 270	Ala	Val
	Ile	Met	Met 275	Val	Thr	Val	Val	Ala 280	Leu	Phe	Ala	Val	Сув 285	Trp	Ala	Pro
25	Phe	His 290	Val	Val	His	Met	Met 295	Ile	Glu	Tyr	Ser	Asn 300	Phe	Glu	ГÀЗ	Glu
	Tyr 305	Asp	Asp	Val	Thr	Ile 310	Lys	Met	Ile	Phe	Ala 315	Ile	Val	Gln	Ile	Ile 320
	Gly	Phe	Ser	Asn	Ser 325	Ile	Cys	Asn	Pro	Ile 330	Val	Tyr	Ala	Phe	Met 335	Asn
30	Glu	Asn	Phe	Lys 340	Lys	Asn	Val	Leu	Ser 345	Ala	Val	Cys	Tyr	Cys 350	Ile	Val
	Asn	Lys	Thr 355	Phe	Ser	Pro	Ala	Gln 360	Arg	His	Gly	Asn	Ser 365	Gly	Ile	Thr
35	Met	Met 370	Arg	Lys	Lys	Ala	Lys 375	Phe	Ser	Leu	Arg	Glu 380	Asn	Pro	Val	Glu
	Glu 385	Thr	Lys	Glγ	Glu	Ala 390	Phe	Ser	Asp	Gly	Asn 395	Ile	Glu	Val	Lys	Leu 400

• •

- 49 -

Cys Glu Gln Thr Glu Glu Lys Lys Leu Lys Arg His Leu Ala Leu Phe Arg Ser Glu Leu Ala Glu Asn Ser Pro Leu Asp Ser Gly His 420 425 5 (40) INFORMATION FOR SEQ ID NO:39: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 24 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39: CTGTGTACAG CAGTTCGCAG AGTG 24 (41) INFORMATION FOR SEQ ID NO:40: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 24 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40: GAGTGCCAGG CAGAGCAGGT AGAC 24 (42) INFORMATION FOR SEQ ID NO:41: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (iv) ANTI-SENSE: NO (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

CCCGAATTCC TGCTTGCTCC CAGCTTGGCC C

10

15

20

25

30

(43) INFORMATION FOR SEQ ID NO:42:

31

w	O	00	31	258

PCT/US99/23687 .

- 50 -

5	(i)	SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: DNA (genomic)	
	(iv)	ANTI-SENSE: YES	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:42:	
TGT	GATC	CT GCTGTCAAAG GTCCCATTCC GG	32
10 (44)	INF	ORMATION FOR SEQ ID NO:43:	
15	(i)	SEQUENCE CHARACTERISTICS: (A) LENGTH: 20 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: DNA (genomic)	
	(iv)	ANTI-SENSE: NO	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:43:	
TCAC	CAATGO	CT AGGTGTGGTC	20
20 (45)	INFO	DRMATION FOR SEQ ID NO:44:	
25	(i)	SEQUENCE CHARACTERISTICS: (A) LENGTH: 22 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: DNA (genomic)	
	(iv)	ANTI-SENSE: YES	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:44:	
TGCA	TAGAC	A ATGGGATTAC AG	22
30 (46)	INFO	DRMATION FOR SEQ ID NO:45:	
	(i)	SEQUENCE CHARACTERISTICS: (A) LENGTH: 511 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single	

. . .

- 51 -

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:
- TCACAATGCT AGGTGTGGTC TGGCTGGTGG CAGTCATCGT AGGATCACCC ATGTGGCACG 60

 5 TGCAACAACT TGAGATCAAA TATGACTTCC TATATGAAAA GGAACACATC TGCTGCTTAG 120

 AAGAGTGGAC CAGCCCTGTG CACCAGAAGA TCTACACCAC CTTCATCCTT GTCATCCTCT 180

 TCCTCCTGCC TCTTATGGTG ATGCTTATTC TGTACGTAAA ATTGGTTATG AACTTTGGAT 240

 AAAGAAAAGA GTTGGGGATG GTTCAGTGCT TCGAACTATT CATGGAAAAG AAATGTCCAA 300

 AATAGCCAGG AAGAAGAAAC GAGCTGTCAT TATGATGGTG ACAGTGGTGG CTCTCTTTGC 360

 10 TGTGTGCTGG GCACCATTCC ATGTTGTCCA TATGATGATT GAATACAGTA ATTTTGAAAA 420

 GGAATATGAT GATGTCACAA TCAAGATGAT TTTTGCTATC GTGCAAATTA TTGGATTTTC 480

 CAACTCCATC TGTAATCCCA TTGTCTATGC A
 - (47) INFORMATION FOR SEQ ID NO:46:
 - (i) SEQUENCE CHARACTERISTICS:

15

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- 20 (iv) ANTI-SENSE: NO
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CTGCTTAGAA GAGTGGACCA G

21

- (48) INFORMATION FOR SEQ ID NO:47:
 - (i) SEQUENCE CHARACTERISTICS:
- 25
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (b) lorobodi: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- 30 (iv) ANTI-SENSE: NO

WO 00/31258		PCT/US99/23687
	- 52 -	

		- 52 -	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:47:	
	CTGTGCAC	CA GAAGATCTAC AC	22
	(49) INF	ORMATION FOR SEQ ID NO:48:	
5		SEQUENCE CHARACTERISTICS: (A) LENGTH: 21 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: DNA (genomic)	
10	(iv)	ANTI-SENSE: YES	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:48:	
	CAAGGATG	aa ggtggtgtag a	21
	(50) INF	DRMATION FOR SEQ ID NO:49:	
15	(i)	SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: DNA (genomic)	
20	(iv)	ANTI-SENSE: YES	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:49:	
	GTGTAGATO	TT TCTGGTGCAC AGG	23
	(51) INFO	ORMATION FOR SEQ ID NO:50:	
25	(i)	SEQUENCE CHARACTERISTICS: (A) LENGTH: 21 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: DNA (genomic)	
30	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:50:	
	GCAATGCAG	G TCATAGTGAG C	21

(52) INFORMATION FOR SEQ ID NO:51:

wo	00/3	1258
----	------	------

- 53 -

(i) 5	SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(ii)	MOLECULE TYPE: DNA (genomic)	
(iii)	HYPOTHETICAL: YES	
(iv)	ANTI-SENSE: YES	
(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:51:	
10 TGGAGCAT	TGG TGACGGGAAT GCAGAAG	2.
(53) IN	FORMATION FOR SEQ ID NO:52:	
(i)	SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(ii)	MOLECULE TYPE: DNA (genomic)	
(iv)	ANTI-SENSE: YES	
(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:52:	
20 gtgatgag	CA GGTCACTGAG CGCCAAG	27
(54) INF	ORMATION FOR SEQ ID NO:53:	
(i) 25	SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(ii)	MOLECULE TYPE: DNA (genomic)	
(iv)	ANTI-SENSE: NO	
(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:53:	
30 GCAATGCA	GG CGCTTAACAT TAC	23
(55) INF	ORMATION FOR SEQ ID NO:54:	
(i)	SEQUENCE CHARACTERISTICS: (A) LENGTH: 22 base pairs	

wo	ΛΛ	/31	258

- 54 -

		(B) TYPE: nucleic acid	
		(C) STRANDEDNESS: single	
		(D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: DNA (genomic)	
5	(iv)	ANTI-SENSE: YES	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:54:	
TTG	GGTTA	CA ATCTGAAGGG CA	22
(56) INF	ORMATION FOR SEQ ID NO:55:	
	(i)	SEQUENCE CHARACTERISTICS:	
10		(A) LENGTH: 23 base pairs	
		(B) TYPE: nucleic acid	
		(C) STRANDEDNESS: single	
		(D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: DNA (genomic)	
15	(iv)	ANTI-SENSE: NO	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:55:	•
ACT	CCGTG!	TC CAGCAGGACT CTG	23
(57) INFO	ORMATION FOR SEQ ID NO:56:	
	(i)	SEQUENCE CHARACTERISTICS:	
20		(A) LENGTH: 24 base pairs	
		(B) TYPE: nucleic acid	
		(C) STRANDEDNESS: single	
		(D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: DNA (genomic)	
25	(iv)	ANTI-SENSE: YES	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:56:	
	(*****)	DESCRIPTION. DESCRIPTION:	
TGC	GTGTTC	CC TGGACCCTCA CGTG	24
(58)	INFO	ORMATION FOR SEQ ID NO:57:	
	(i)	SEQUENCE CHARACTERISTICS:	
30		(A) LENGTH: 29 base pairs	
		(B) TYPE: nucleic acid	
		(C) STRANDEDNESS: single	

WO 00/31258	W	O	00	/31	1258
-------------	---	---	----	-----	------

- 55 -

- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: NO
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

CAGGCCTTGG ATTTTAATGT CAGGGATGG

29

- 5 (59) INFORMATION FOR SEQ ID NO:58:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27 base pairs
 - (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single (D) TOPOLOGY: linear
- 10
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (iv) ANTI-SENSE: YES
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

GGAGAGTCAG CTCTGAAAGA ATTCAGG

27

- 15 (60) INFORMATION FOR SEQ ID NO:59:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
- 20 (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (iv) ANTI-SENSE: NO
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

TGATGTGATG CCAGATACTA ATAGCAC

27

- 25 (61) INFORMATION FOR SEQ ID NO:60:
 - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
- 30
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: YES

w	a	nn	/31	258

- 56 -

		·	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:60:	•
CCTG	ATTC	AT TTAGGTGAGA TTGAGAC	27
(62)	INFO	DRMATION FOR SEQ ID NO:61:	
5	(i)	SEQUENCE CHARACTERISTICS: (A) LENGTH: 22 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: DNA (genomic)	
10	(iv)	ANTI-SENSE: NO	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:61:	
GACA	GGTAC	CC TTGCCATCAA G	21
(63)	INFO	ORMATION FOR SEQ ID NO:62:	
15	(i)	SEQUENCE CHARACTERISTICS: (A) LENGTH: 22 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: DNA (genomic)	
20	(iv)	ANTI-SENSE: YES	
1	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:62:	
CTGC	ACAAT	G CCAGTGATAA GG	22
(64)	INFO	RMATION FOR SEQ ID NO:63:	
25	(i)	SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
((ii)	MOLECULE TYPE: DNA (genomic)	
30	(iv)	ANTI-SENSE: NO	
((xi) :	SEQUENCE DESCRIPTION: SEQ ID NO:63:	
CTGAC	TTCT	T GTTCCTGGCA GCAGCGG	27

. . .

- 57 -

(65) II	NFORMATION FOR SEQ ID NO:64:	
5	i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(i.i	i) MOLECULE TYPE: DNA (genomic)	
(iv	r) ANTI-SENSE: YES	
ix)	i) SEQUENCE DESCRIPTION: SEQ ID NO:64:	
10 AGACCAG	SCCA GGGCACGCTG AAGAGTG	27
(66) II	FORMATION FOR SEQ ID NO:65:	
. (i	.) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(ii	.) MOLECULE TYPE: DNA (genomic)	
(iv	r) ANTI-SENSE: NO	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:	
20 GATCAAG	CTT CCATCCTACT GAAACCATGG TC	32
(67) IN	FORMATION FOR SEQ ID NO:66:	
(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 35 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(ii	.) MOLECULE TYPE: DNA (genomic)	
(iv	ANTI-SENSE: YES	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:	

(68) INFORMATION FOR SEQ ID NO:67:

30 GATCAGATCT CAGTTCCAAT ATTCACACCA CCGTC

(i) SEQUENCE CHARACTERISTICS:

```

35

- 58 -

| (A) | LENGTH: | 22 | base | pairs |
|-----|---------|----|------|-------|
|-----|---------|----|------|-------|

- (B) TYPE: nucleic acid(C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- 5 (ii) MOLECULE TYPE: DNA (genomic)
  - (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

#### CTGGTGTGCT CCATGGCATC CC

22

#### (69) INFORMATION FOR SEQ ID NO:68:

- 10 (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 22 base pairs
  - (B) TYPE: nucleic acid(C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- 15 (ii) MOLECULE TYPE: DNA (genomic)
  - (iv) ANTI-SENSE: YES
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

### GTAAGCCTCC CAGAACGAGA GG

22

- (70) INFORMATION FOR SEQ ID NO:69:
- 20 (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 24 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: DNA (genomic)
  - (iv) ANTI-SENSE: NO
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

#### CAGCGCAGGG TGAAGCCTGA GAGC

24

. .. .. . .

- (71) INFORMATION FOR SEQ ID NO:70:
- 30 (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 24 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- 59 -

(ii) MOLECULE TYPE: DNA (genomic) (iv) ANTI-SENSE: YES (xi) SEQUENCE DESCRIPTION: SEQ ID NO:70: GGCACCTGCT GTGACCTGTG CAGG 24 5 (72) INFORMATION FOR SEQ ID NO:71: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 22 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (iv) ANTI-SENSE: NO (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71: GTCCTGCCAC TTCGAGACAT GG 22 15 (73) INFORMATION FOR SEQ ID NO:72: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (iv) ANTI-SENSE: YES (xi) SEQUENCE DESCRIPTION: SEQ ID NO:72: GAAACTTCTC TGCCCTTACC GTC 23 25 (74) INFORMATION FOR SEQ ID NO:73:

10

20

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

30 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

- 60 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

CCAACACCAG CATCCATGGC ATCAAG

26

(75) INFORMATION FOR SEQ ID NO:74:

- (i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 27 base pairs

  - (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- 10 (iv) ANTI-SENSE: YES

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

GGAGAGTCAG CTCTGAAAGA ATTCAGG

27